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(58) Field of Search
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(71) Applicant(s)
Kotobuki Pharmaceutical Company Limited
(Incorporated in Japan)
6531 Oaza-Sakaki, Sakaki-Machi, Hanishina-Gun, Nagano-Ken, Japan

(72) Inventor(s)
Tsuyoshi Tomiyama
Akira Tomiyama
Hiroshi Tomiyama
Keiko Kuroiwa

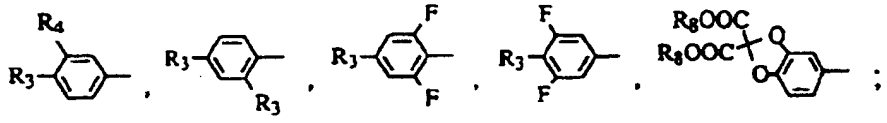
(74) Agent and/or Address for Service
J A Kemp & Co.
14 South Square, Gray's Inn, LONDON, WC1R 5LX, United Kingdom

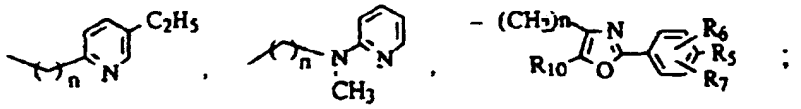
(54) Abstract Title
Antidiabetic ether and amide compounds

(57) A compound of formula (I),

$$R_1\text{-}A\text{-}R_2 \qquad (I)$$

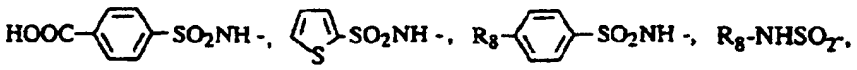
wherein A is -O- or $-NH-\overset{O}{\overset{\|}{C}}-$;

R_1 is  ;

R_2 is  ;

R_3 is OH-, CH_3SO_2NH-, CF_3SO_2NH-, $CH_3SO_2NHCH_2$-, $CF_3SO_2NHCH_2$-,

HOOC-, CH_3OOC-, R_8-OOC-$\overset{O}{\overset{\|}{C}}$-NH-, HOOC-$CH_2SO_2NH$-, CF_3-CH_2SO_2NH-,



(57) continued overleaf

This print incorporates corrections made under Section 117(1) of the Patents Act 1977.

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(57) cont

R_8-$NHSO_2$-CH_2-, HOOC-CH_2-O-, HSO_3N=CH-, or R_9-SO_2NHCO-;
R_4 is H, OH, O-alkyl or O-CH_2OCH_3;
R_5 is H, halogen, -CH_2COOH or OH;
R_6 and R_7 are halogen, t-butyl or pyrrolidyl;
R_8 is hydrogen or lower alkyl;
R_9 is alkyl or thienyl;
R_{10} is lower alkyl,
or a pharmaceutically acceptable salt thereof,

with the provisos that (i) when A is -O-, then n is 2 or 3, and (ii) when A is $-NH-\overset{\overset{O}{\|}}{C}-$, then n is 1 or 2, are useful as antidiabetic agents. Synthetic preparations of the compounds of the invention are disclosed as are pharmaceutical compositions containing such compounds.

SPECIFICATION

TITLE OF THE INVENTION

ETHER AND AMIDE COMPOUNDS AND PREPARATION OF THEREOF AS ANTIDIADETICS.

BACKGROUND OF THE INVENTION

Field of the Invention

This invention is regarding to new ether and/or amide derivatives which are useful for the treatment of diabetes and a pharmaceutical composition containing these compounds as active ingredients.

Current Technology

Biguanide and sulfonyl urea derivatives have been used as anti-diabetics so far. But these compounds have some drawbacks. For instance, biguanide compounds cause diabetic acidosis and sulfonyl urea compounds often cause hypoglycemia and it is required to be careful for taking these drugs.

Recently, thiazolidine-2,4-dion derivatives are reported to have blood glucose lowering activities.

For example, Troglitazone (T.Yoshioka et al.,J.Med.Chem.1989,32,421), Pioglitazone (H.Ikeda et al., J.Med.Chem.1992,35,2617) or Rosiglitazone (B.C.C.Cantello et al., J.Med.Chem.1994,37, 3977) are mentioned as Thiazolidine-2,4-dione derivatives and Troglitazone is applied for clinical use.

However, these thiazolidime-2,4-dione compound are reported to cause of liver toxicity (R.Perfetti et al.,Diabetes/Metabolism Review 1998,14(3),207) and further, side effect to troglitazone treatment have been reported. They include cardiomegaly and hepatic malfunction such as increasements of amino transferase (AST), alanin transferees (ALT), and lactic dehydrogenase (LDH). (R.R.Henry, Endocrinol.Metab,Clin,North Am.1997,26,553)

To alleviate the side effect of thiazolidine-2,4-dione derivatives, several non-thiazolidine-2,4-diones are reported such as oxazoline-2,4-diones are reported such as oxazoline-2,4-dione (R.L.Dow et al.,J.Med.Chem.1991,34,1538), 1-oxo-2,4-diazoline-3,5-dione (S.W.Goldstein et al., J.Med.Chem.1993,36,2238), α -amino carboxylic acid (R.A.DeFronzo,Diabetes,1988,37,667), and Dicarboxylic acid ester (H.Shinkai et al., J.Med.Chem.1998,41,1927)

The Subject of Invention

The present invention concerns ether and amide compounds which enhance insulin action and show hypoglycemic activity with low toxicities and a pharmaceutical composition containing these compounds as active ingredients.

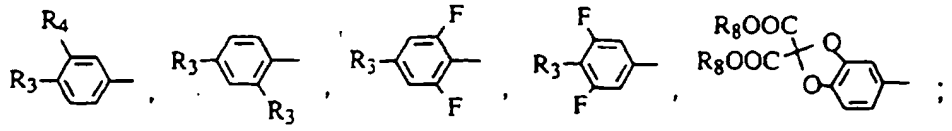
A Solution to the Problem

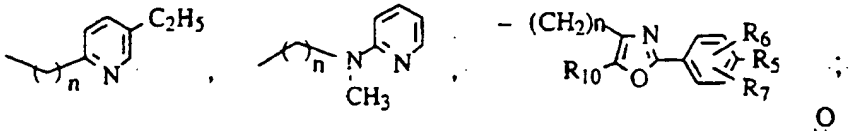
After elaborated to make an anti-diabetic drug, the inventors found that new compounds as show general formula (I) had shown potent anti-diabetic activities and fulfilled this invention.

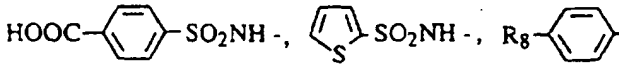
Namely, the invention is the compounds as shown in general formula (I) and its pharmaceutically acceptable salts and a composition containing these compounds as active ingredients.

R_1—A—R_2 ———————— (I)

wherein A is —O— or —NH—C(=O)— ;

R_1 is  ;

R_2 is  ;

(with the provisos that (i) when A is -O- , then n is 2 or 3 (ii) when A is —NH—C(=O)— , then n is 1 or 2. R_3 is OH-, CH_3SO_2NH-, CF_3SO_2NH-, $CH_3SO_2NHCH_2$-, $CF_3SO_2NHCH_2$-, HOOC-, CH_3OOC-, R_8-OOC-C(=O)-NH-, HOOC-CH_2SO_2NH-, CF_3-CH_2SO_2NH-,  , R_8-$NHSO_2$-, R_8-$NHSO_2$-CH_2-, HOOC-CH_2-O-, HSO_3N=CH-, or R_9-SO_2NHCO-;

R_4 is H, OH, O-alkyl or O-CH_2OCH_3;

R_5 is H, halogen atom, -CH_2COOH or OH;

R_6 and R_7 are hydrogen, t-butyl or pyrolidyl;

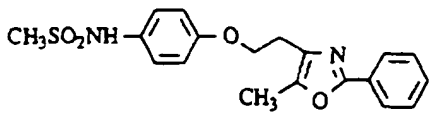
R_8 is hydrogen or lower alkyl ;

R_9 is alkyl or thienyl ;

R_{10} is lower alkyl)

Enforcement of Invention

70 compounds are exemplified as follow, but the invention is not limited to these compounds. Further the preparation of the compounds 1 - 70 are exemplified in each experimental sections.



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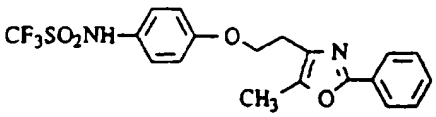

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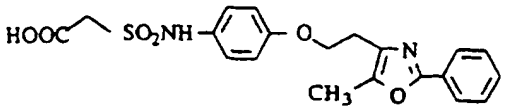

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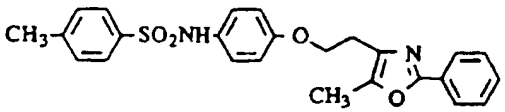

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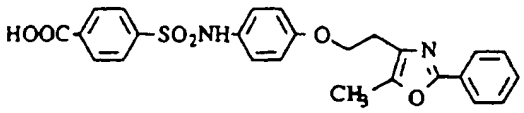

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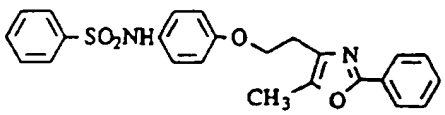

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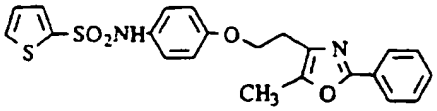

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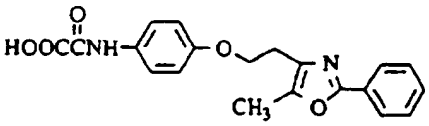

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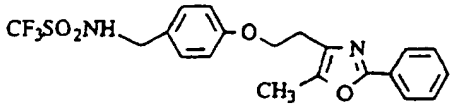

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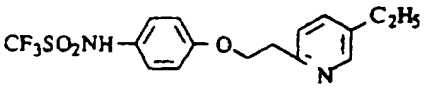

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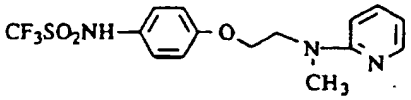

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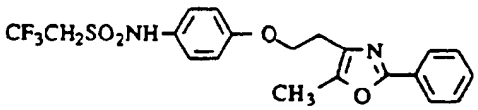

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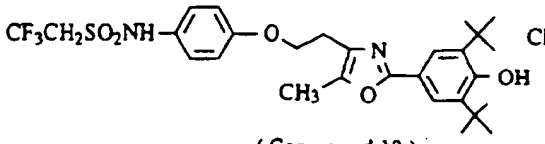

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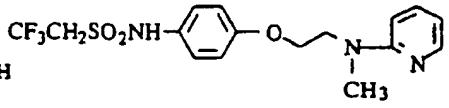

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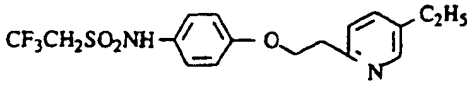

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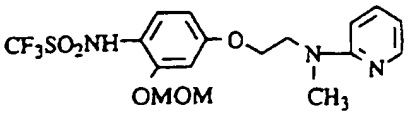

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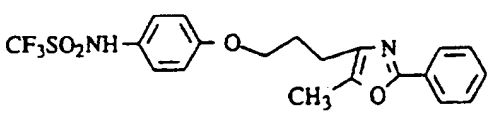

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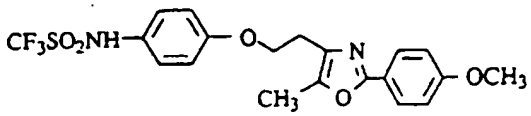

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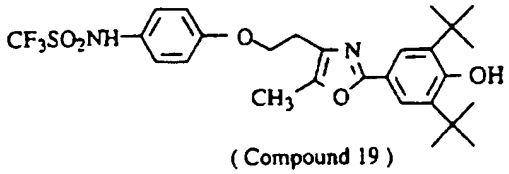

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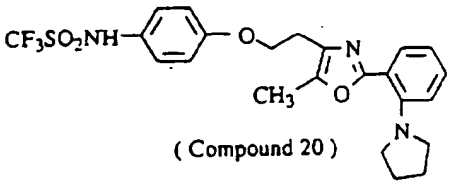

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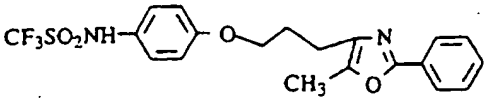

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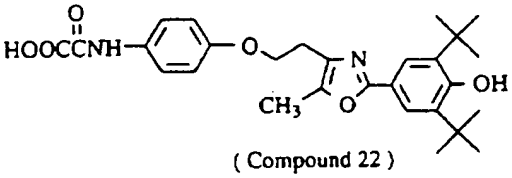

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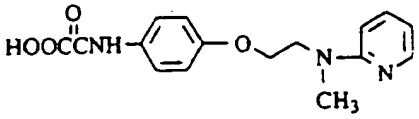

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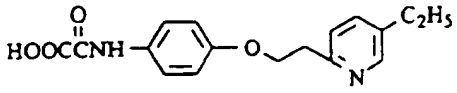

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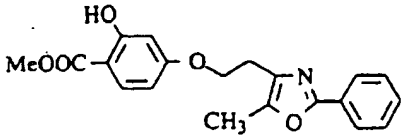

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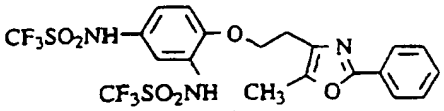

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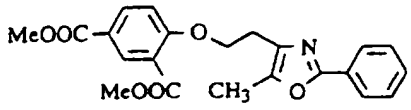

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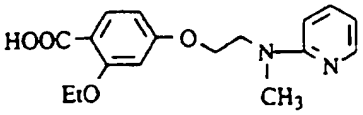

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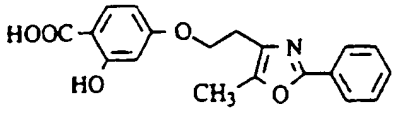

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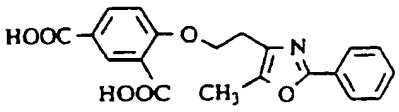

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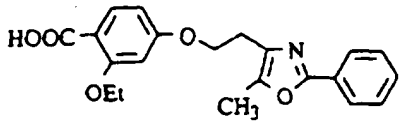

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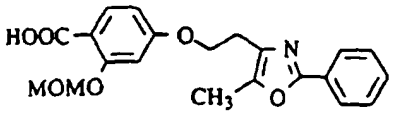

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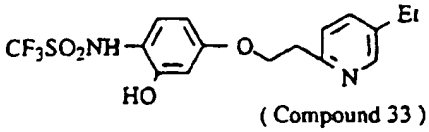

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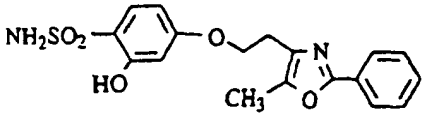

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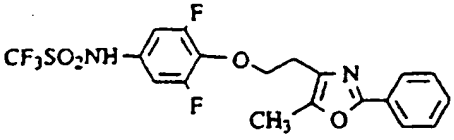

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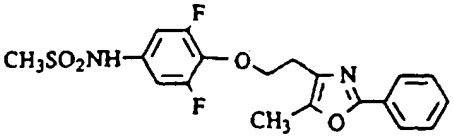

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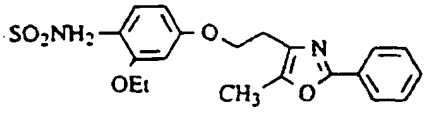

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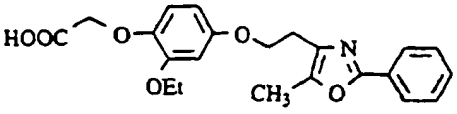
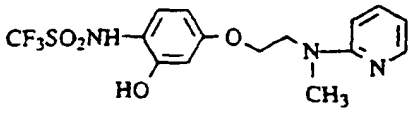
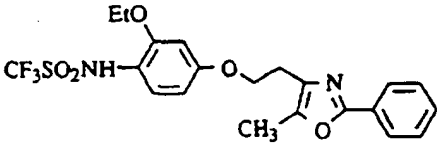


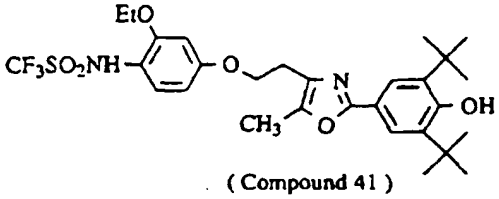
(Compound 38)



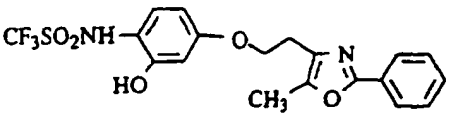
(Compound 39)



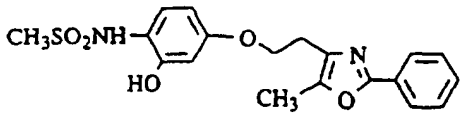
(Compound 40)



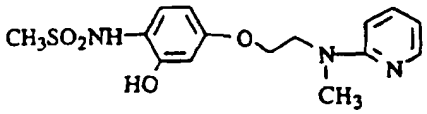
(Compound 41)



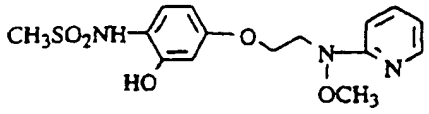
(Compound 42)



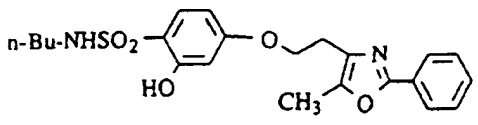
(Compound 43)



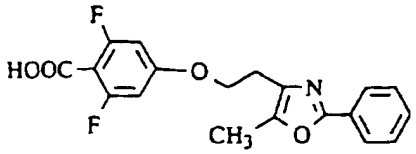
(Compound 44)



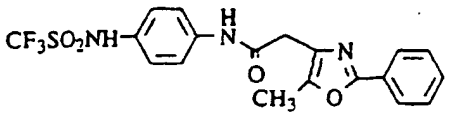
(Compound 45)



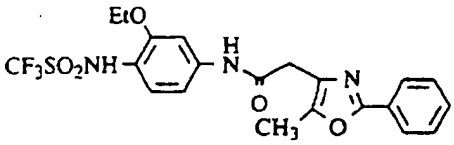
(Compound 46)



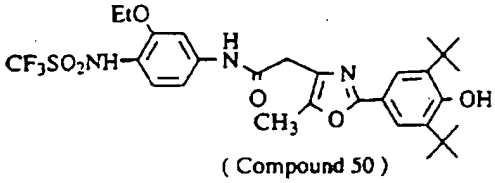
(Compound 47)



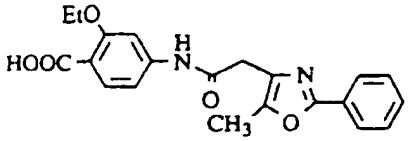
(Compound 48)



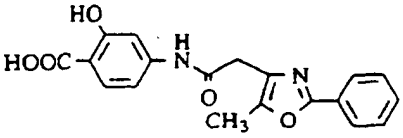
(Compound 49)



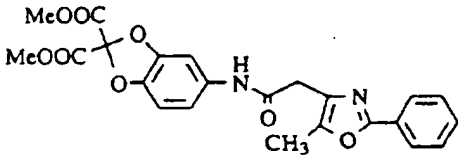
(Compound 50)



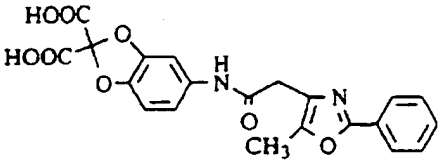
(Compound 51)



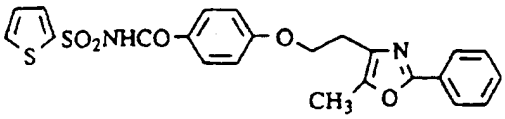
(Compound 52)



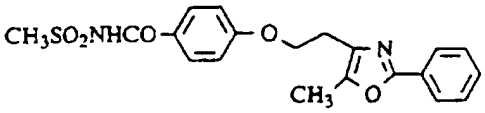
(Compound 53)



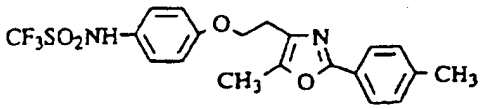
(Compound 54)



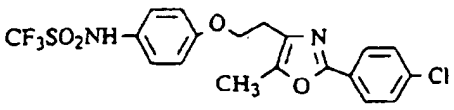
(Compound 55)



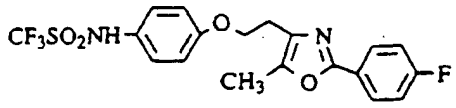
(Compound 56)



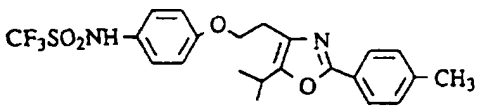
(Compound 57)



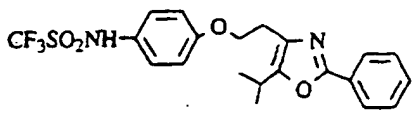
(Compound 58)



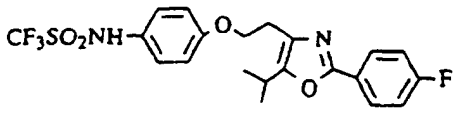
(Compound 59)



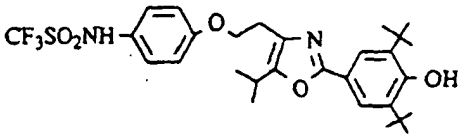
(Compound 60)



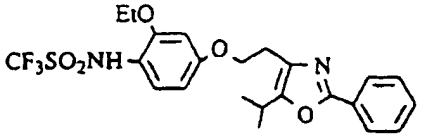
(Compound 61)



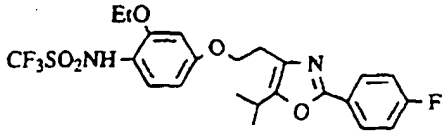
(Compound 62)



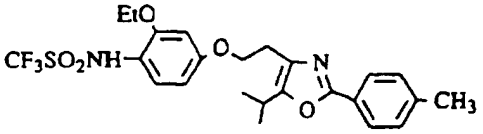
(Compound 63)



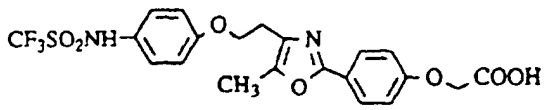
(Compound 64)



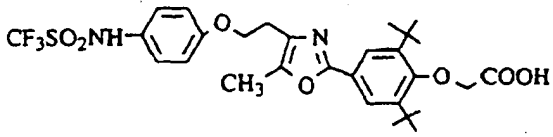
(Compound 65)



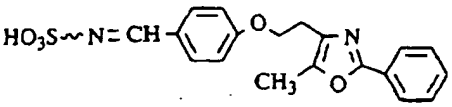
(Compound 66)



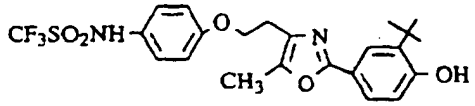
(Compound 67)



(Compound 68)



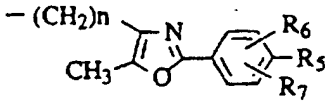
(Compound 69)



(Compound 70)

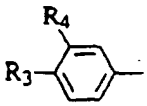
Typical preparations of the compounds of general formula (I) according to the invention are shown.

(I) The preparation of a compound of general formula (I) in which

A is -O- ; R_2 is  ;

(wherein : R_5, R_6, and R_7 have the above-mentioned meanings; n=2)

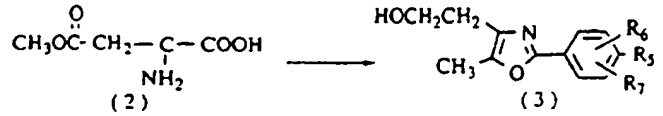
(a) In case of

R_1 is 

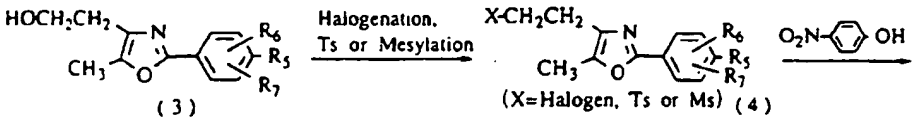
in which R_3 is CH_3SO_2NH- or CF_3SO_2NH- and R_4 is H.

The compounds can be obtained by means of the following reaction diagram: Asparatic acid ß-methyl ester (2). (J.Arg.Chem.Soc.Japan,1951-1952,25,129):C.A.47,6065i or R.L.Prestige et al.,

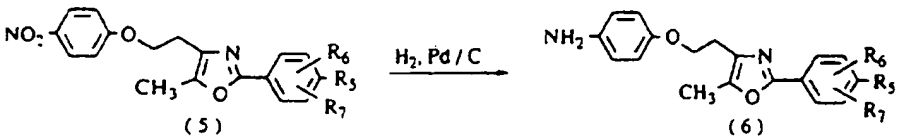
J.Org.Chem.1975,40,3287 as a starting material is converted to compound (3) by the known method (B.Helvin et al.,J.Med.Chem.1992,35,1853) and compound (3) is tosylated or mesylated to obtain compound (4). The coupling reaction of compound (4) with nitrophenol to obtain compound (5) and then compound (5) is reduced with H_2-Pd/C to obtain compound (6) and compound (6) is subjected to react with several sulfonyl chloride (7) and sulfonic acid anhydride (8) to obtain the compound of genaral formula (I).



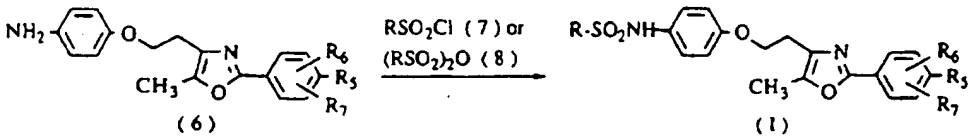
(2) (3)



(3) (X=Halogen, Ts or Ms) (4)

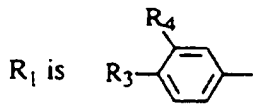


(5) (6)



(6) (I)

(b) In case of

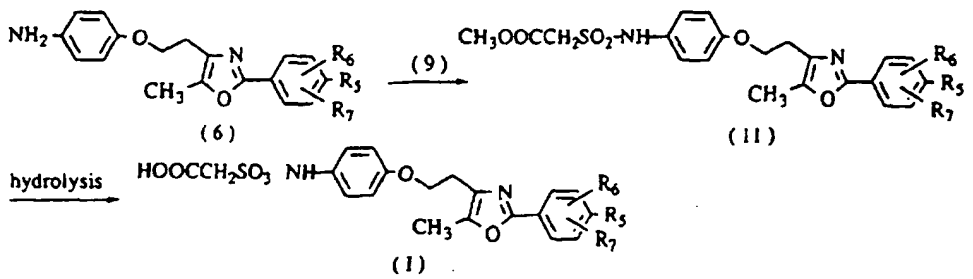


in which R_3 is $HOOCCH_2SO_2NH$- and R_4 is H.

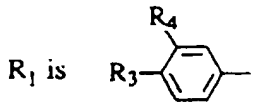
The compounds can be obtained by mean of the following reaction diagram :

The reaction of compound (6) and $EtOOC{\cdot}CH_2SO_2Cl$ as a sulfonyl chloride, namely $CH_3OOCCH_2SO_2Cl$ (9), to obtain the ester (11) and then compound (11) is hydrolyzed to obtain the compound of genaral formula (I).

The above mentioned compound (9) is obtained by the chlorination of sulfoacetic acid ($HOOCCH_2SO_3H$(10)) with $SOCl_2$ and then reacted with alcohol (R.L.Hinman et al. (J.Am.Chem. Soc. 1959,81,5655), (H.T.Lee et al.,Bioorg.Med.Chem.Lett.1998,8,289)



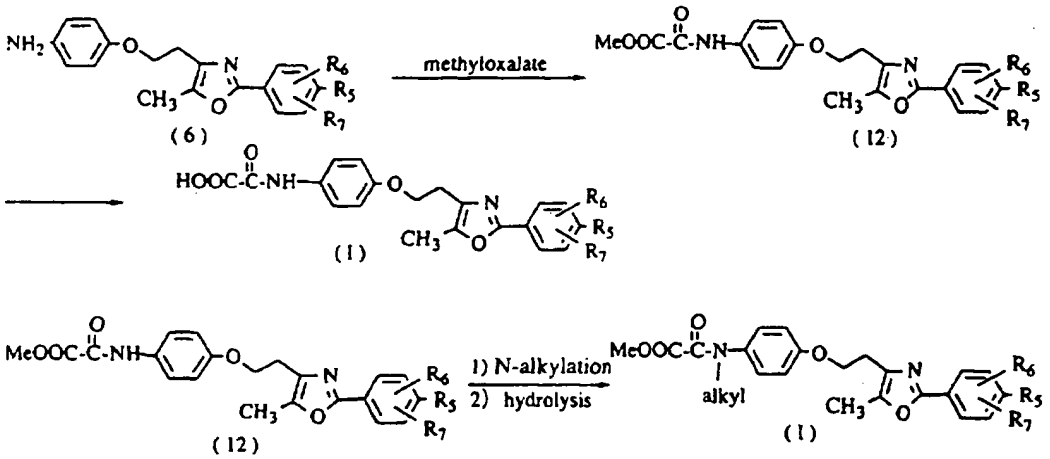
(c) In case of



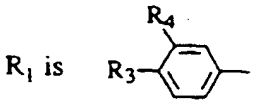
in which R3 is HOOC-CONH- and R4 is H.

The compound can be obtained by means of the following reaction diagram :

The reaction of compound (6) and methyloxalate to obtain compound (12) and compound (12) is hydrolyzed to obtain the compound of general formula (I). Further compound (12) is N-alkylated with alkylhalide and ther subjected to hydrolyze to obtain the compound of general formula (I).



(d) In case of

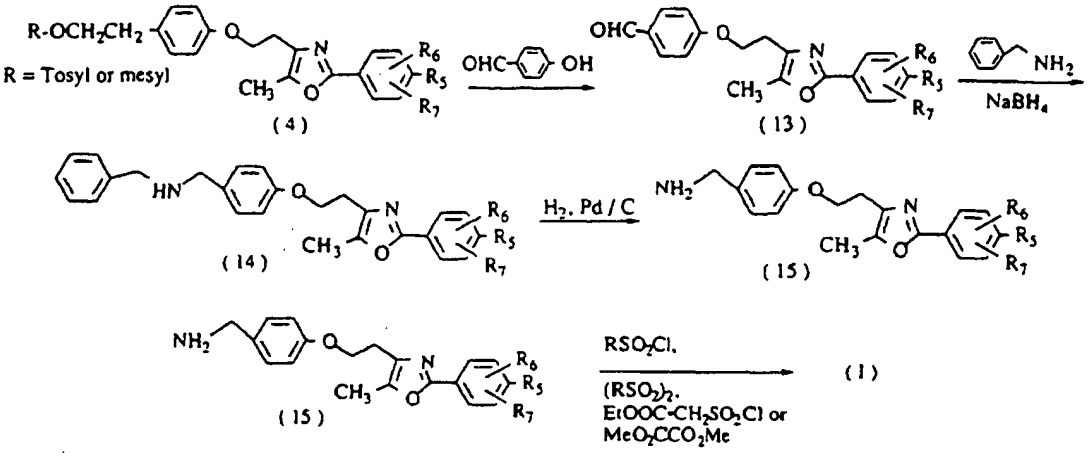


in which R3 is $CH_3SO_2NHCH_2$-, CF_3SO_2 $NHCH_2$- and HOOC-CONH-, and R4 is H.

The compound can be obtained by means of the following reaction diagram :

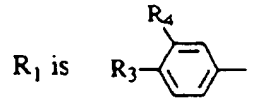
Compound (4) is reacted with p-hydroxy benzaldehyde to obtain compound (13) and compound (13) is subjected to reductive amination using benzylamine and sodium borohydride to obtain compound (14).

After debenzylation of compound (14) in H_2-Pd/C, compound (15) is obtained. Compound (15) is reacted with sulfonyl chloride, sulfonic acid anhydride, $EtOOC{\cdot}CH_2SO_2Cl$ or methyloxalate as the same manner as in case of compound (6) and compound (12), then the compound of general formula (I) is obtained.



(4) (13) (14) (15) (15) (I)

(e) In case of

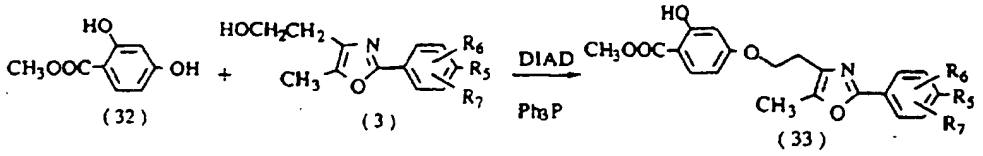


R_1 is

in which R_3 is HOOC- or CH_3OOC- and R_4 is -OH or -O-alkyl.

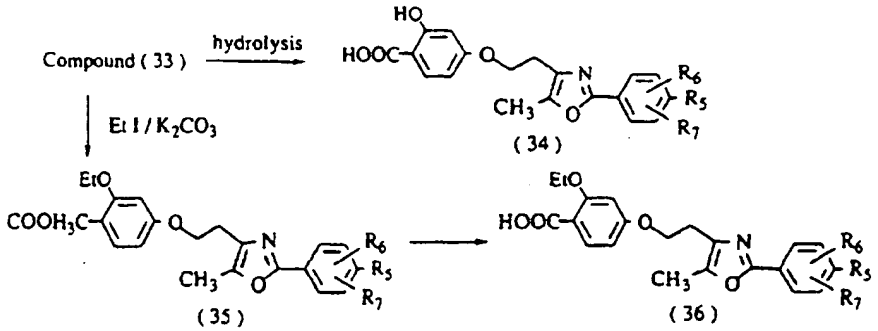
As shown in the following reaction diagram,

compound (32) and compound (3) is subjected to the MITSUNOBU reaction to obtain the compound (33) which is the compound of general formula (I).



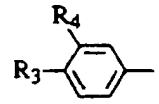
(32) (3) (33)

Further, compound (33) can be converted to compound (34) and compound (36) as shown in the following diagram.



(34) (35) (36)

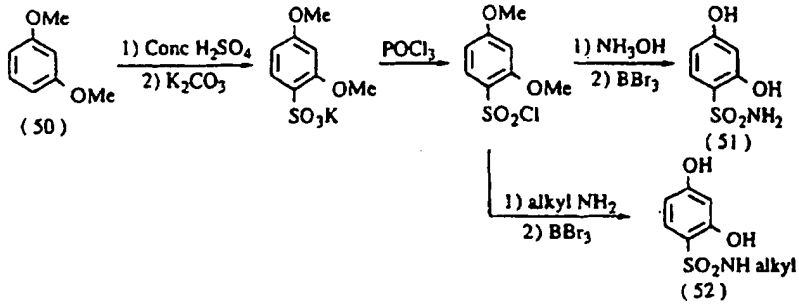
(f) In case of

R_1 is 

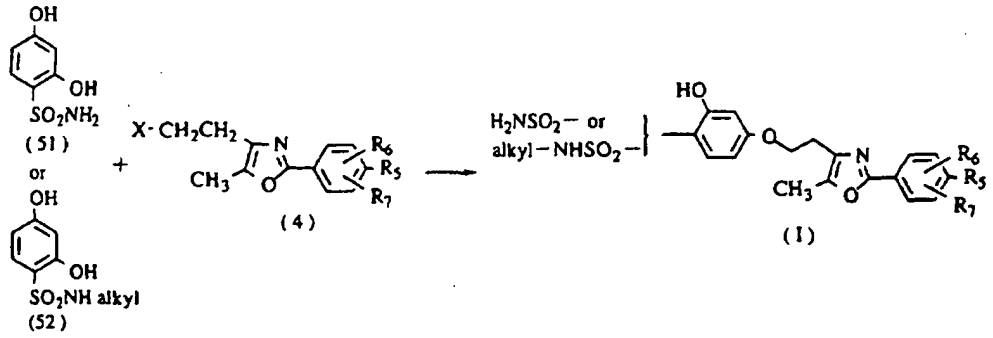
in which R_3 is NH_2SO_3- or alkyl-$NHSO_2$ - and R_4 is -OH.

As shown in the following reaction diagram,

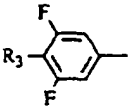
according to the literature method (J.Med.Chem.1997,20,1235), compound (51) and (52) are obtained from resorcin dimethyl ether (50).



Further, obtained compounds (51) and (52) are reacted with compound (4) to obtain general formula (I) as follow.



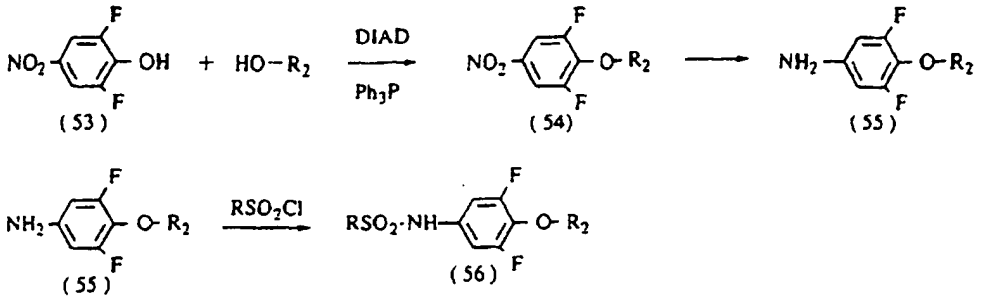
(g) In case of

R_1 is 

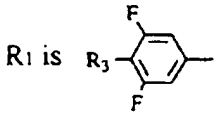
in which R_3 is CH_3SO_2NH- or CF_3SO_2 NH-.

As shown in the following reaction diagram,

compound (53) is subjected to the MITSUNOBU reaction to obtain compound (54) and reduction of compound (54) yields compound (55). Compound (55) is converted to compound (56) according to the method of the preparation of compound (42) from compound (39).



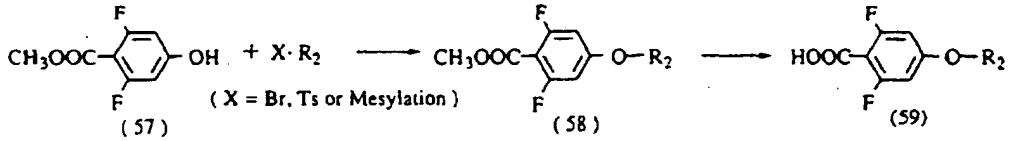
(h) In case of



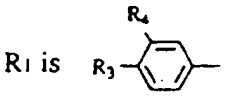
in which R3 is -COOH.

As shown in the following reaction diagram,

compound (57) is reacted with compound (4) and obtain the ether compound (58) and the resulting compound (58) is hydrolyzed to obtain compound (59) which is the compound of general formula (I).



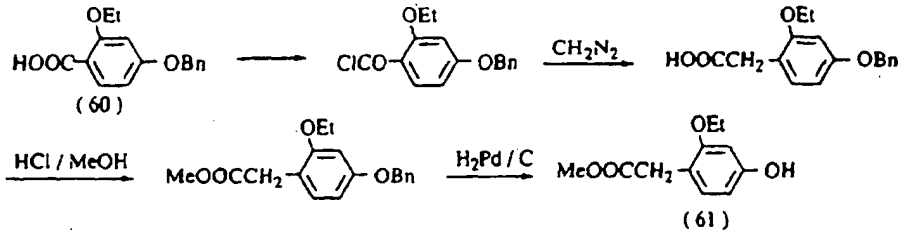
(i) In case of

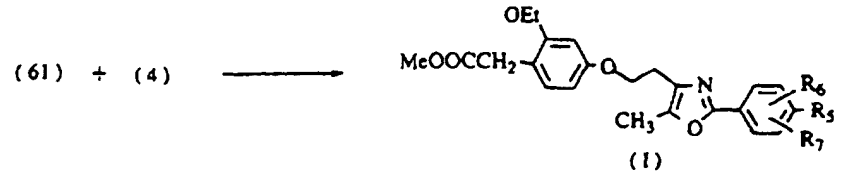


in which R3 is $MeOOCCH_2$- , and R4 is -O-alkyl.

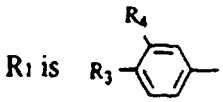
As shown in the following reaction diagram,

compound (61), which is obtained from compound (60), is reacted with compound (4) to obtain the compound of general formula (I).





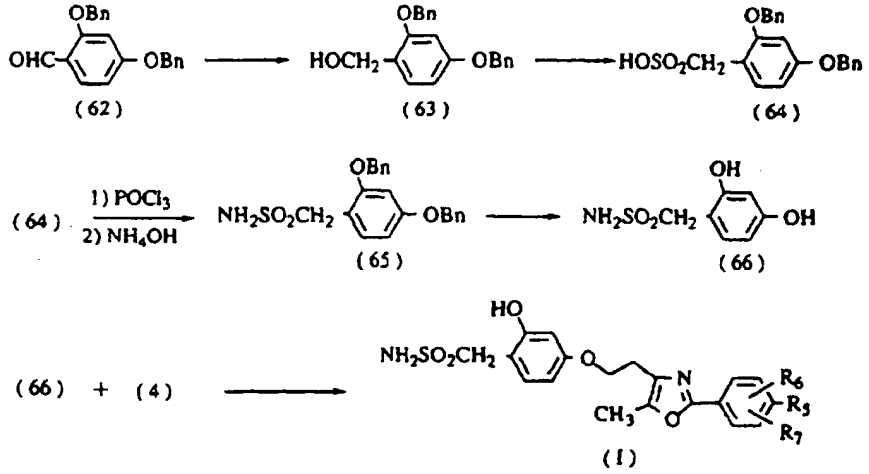
(j) In case of



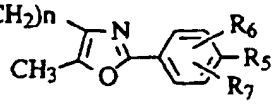
in which R_3 is $NH_2SO_2CH_2$- or alkyl-$NHSO_2CH_2$- and R_4 is OH or -O-alkyl.

As shown in the following reaction diagram,

after reduction of compound (62), the obtained compound (63) is reacted with Na_2SO_3 to obtain compound (64) according to the reported method (J.C.S.Chem.Comom.,1989,521). Then compound (64) is chlorinated with $POCl_3$ and treated with aqueous NH_3 to obtain the amide compound (65). After debenzylation of compound (65), compound (66) is obtained. Compound (66) is reacted with compound (4) to yield the compound of general formula (I).

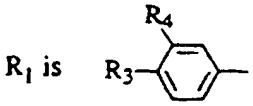


(II) The preparation of a compound of general formula (I) in which

A is -O- ; R_2 is  ;

(wherein : R_5, R_6, and R_7 have the above mentioned meaning; n=3)

(a) In case of

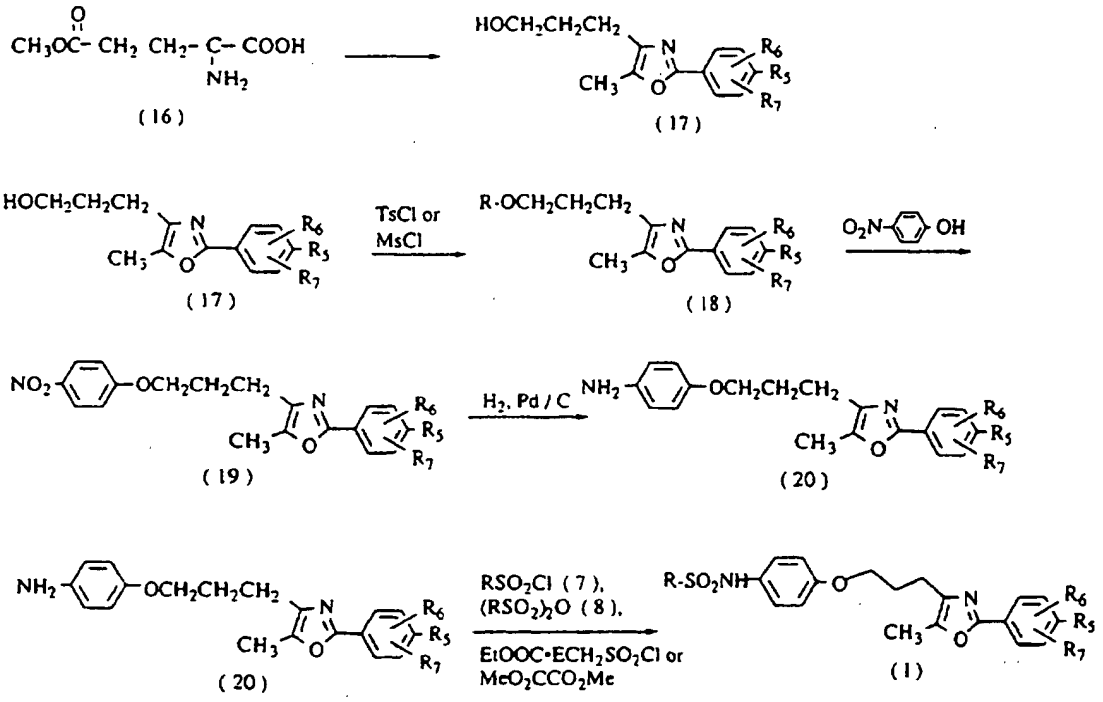


in which R_3 is CH_3SO_2NH- or CF_3SO_2NH-, and R_4 is H.

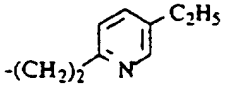
As shown in the following reaction diagram,

glutamic acid γ -methyl ester (16) is used in stead of aspartic acid ß-methyl ester (2). Compound (17) is obtained from compound (16) by the same method as compound (3) is obtained from compound (2).

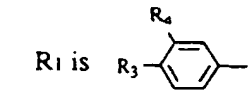
After compound (17) is halogenated, tosylated or mesylated, obtained compound (18) is coupled with nitrophenol and the resulting compound (19) is hydrogenated to obtain compound (20). The obtained compound (20) is reacted with several sulfonyl chlorides, sulfonic acid anhydrides, EtOOC·CH_2SO_2Cl or methyloxalate to obtain the compound of general formula (I).



(III) The preparation of a compound of general formula (I) in which

A is -O- ; R_2 is 

(a) In case of

R_1 is 

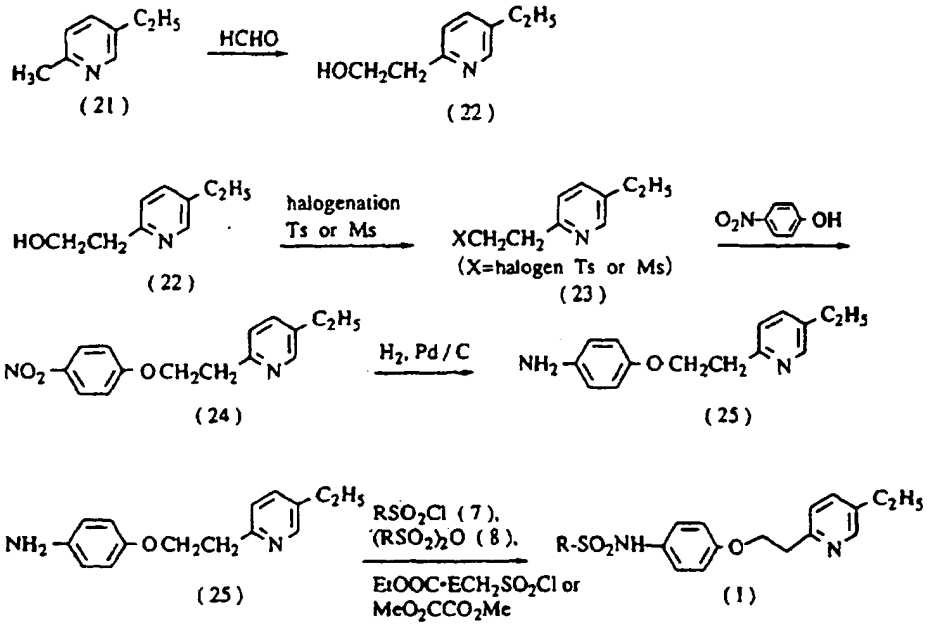
in which R_3 is CH_3SO_2NH- or CF_3SO_2NH- , and R_4 is H.

As shown in the following reaction diagram,

after the reaction of 2-methyl 5-ethylpyridine (21) and formaldehyde using the reported method

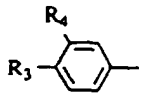
(Japanese Patent Publication,1981-65870), compound (22) is obtained. After compound (22) is halogenated, tosylated or mesylated, obtained compound (23) is coupled with nitrophenol and the resulting compound (24) is hydrogenated to obtain compound (25), by the same method as compound (4) is obtained from compound (3).

The obtained compound (25) is reacted with several sulfonylchlorides (7), sulfonic acid anhydrides (8), $EtOOC{\cdot}CH_2SO_2Cl$ or methyloxalate to obtain the compound of general formula (I).



(21) (22) (22) (23) (24) (25) (25) (1)

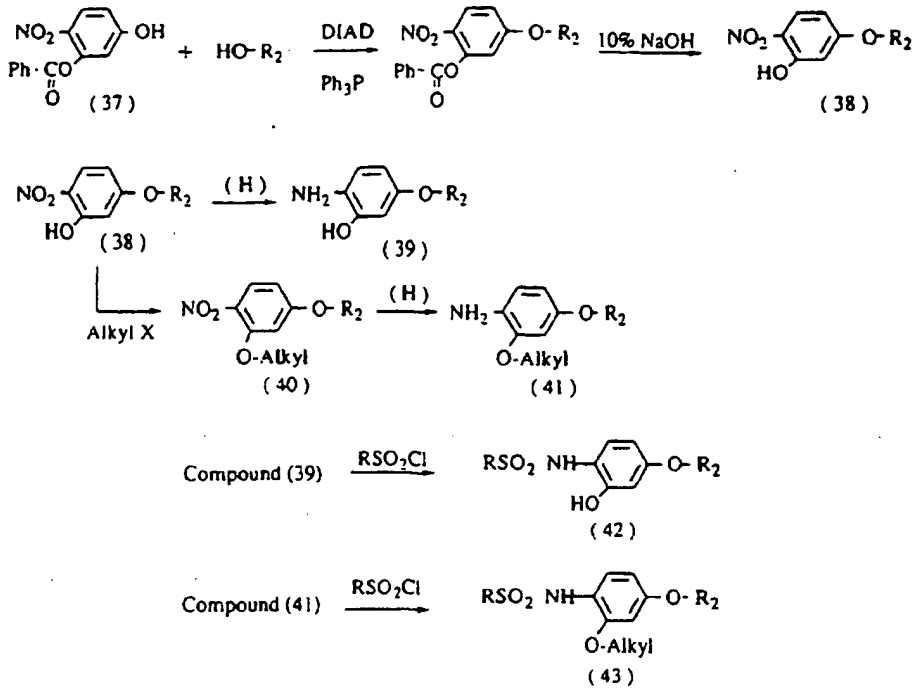
(b) In case of

R_1 is 

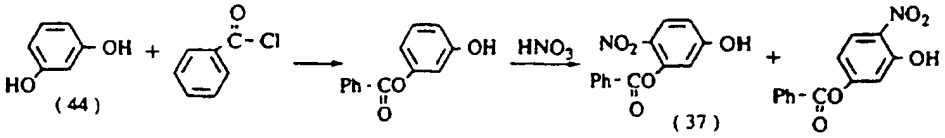
in which R_3 is CH_3SO_2NH- or CF_3SO_2NH- , and R_4 is -OH or -O-alkyl.

As shown in the following reaction diagram,

compound (37) is reacted with HO-R_2 to obtain compound (38) and compound (38) is hydrogenated to compound (39), or compound (38) is alkylated to compound (40) and reduction of compound (40) is resulting compound (41) . Then compound (39) or (41) are reacted with RSO_2Cl and obtain compound (42) or compound (43).



Compound (37) in the diagram can be obtained from resorcin as follow.

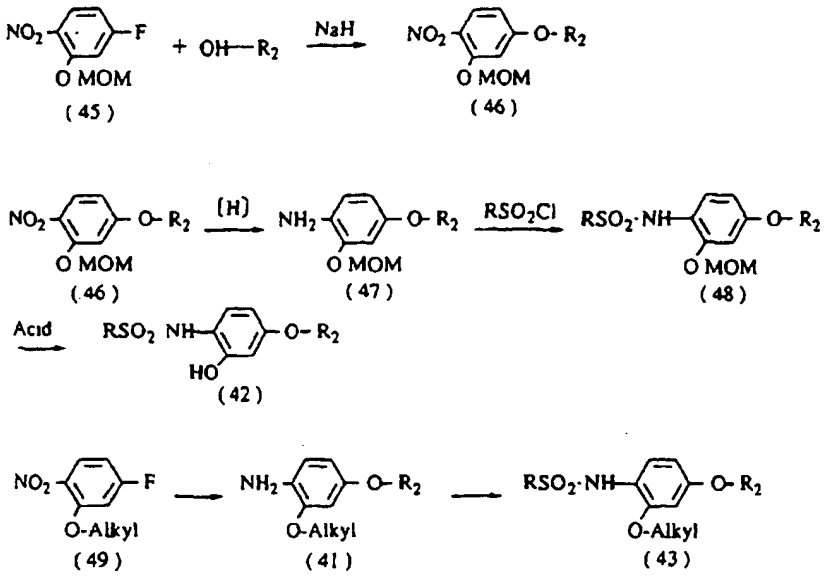


And compound (42) and (43) can be obtained by using the reported method of coupling reaction of fluorobenzene and alcholol (Bioorg.Med.Chem.Lett.,1994,4 (10),1181). Namely, 2-OMOM (methoxy methyl)-4-fluoro nitrozenzene (45) is reacted with HO-R2 to give compound (46) and resulting compound (46) is reduced to obtain compound (47).

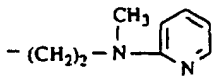
Compound (47) is reacted with RSO_2Cl to obtain compound (48) and after deprotection of MOM-group in compound (48), compound (42) is obtained.

Instead of compound (45), compound (49) is also converted to compound (41), and compound (43) is obtained from compound (41) by the same method as compound (48) is obtained from compound (46).

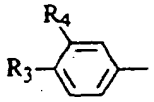
The process is shown in the following reaction diagram.



(IV) The preparation of a compound of general formula (I) in which

A is -O- ; R_2 is 

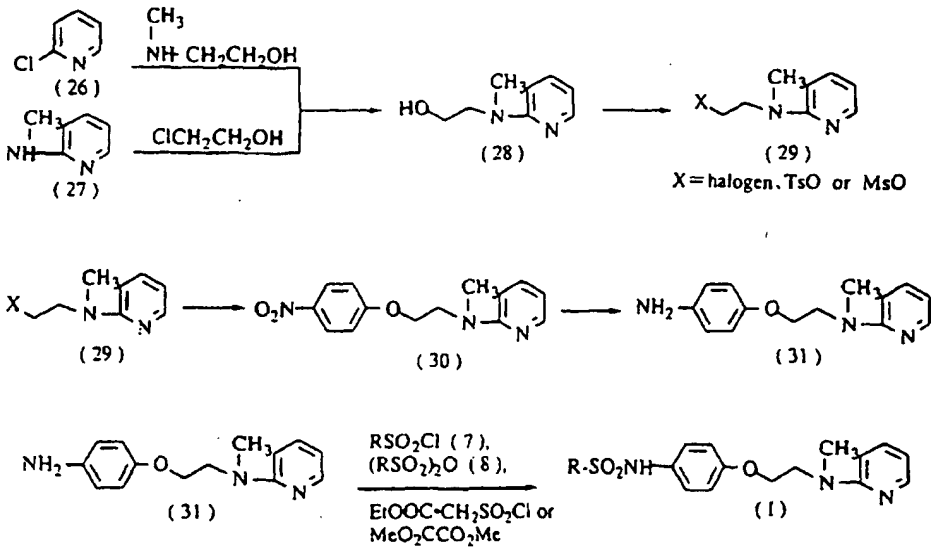
(a) In case of

R_1 is 

in which R_3 is CH_3SO_2NH- or CF_3SO_2NH- , and R_4 is -H.

As shown in the following reaction diagram,

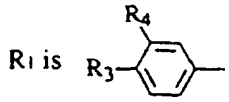
compound (28), obtained from 2-chloropyridine (26) or 2-methyl amino pyridine (27), is tosylated or mesylated to obtain compound (29). Compound (29) is subjected to coupling reaction with nitro phenol and obtained compound (30) using the same manner to obtain compound (3). Resulting compound (30) is reduced to obtain compound (31) and compound (31) is reacted several sulfonyl chlorides (7), sulfonic acid anhydrides (8), $EtOOC{\cdot}CH_2SO_2Cl$ and methyloxalate to obtain the compound of general formula (I).



(V) The preparation of a compound of general formula (I) in which

A is -NH-CO-

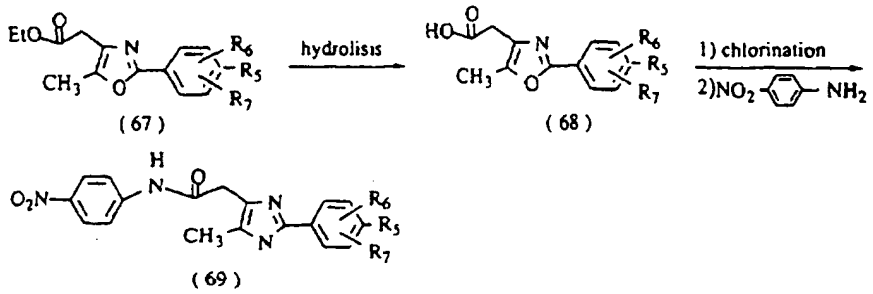
(a) In case of



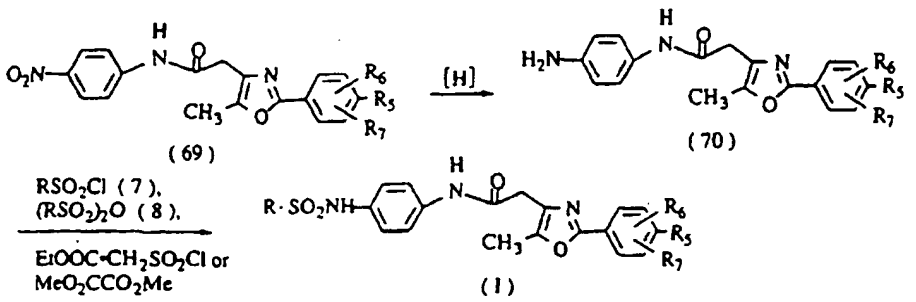
in which R_3 is CH_3SO_2NH- or CF_3SO_2NH- , and R_4 is -H.

As shown in the following reaction diagram,

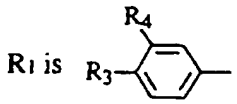
compound (67), intermediate for compound (3), is obtained according to the reported method (J.Med.Chem.1999,35,1853) and compound (67) is hydrolyzed to obtain compound (68). After chlorination of compound (68), obtained chloride is reacted with p-nitroaniline to obtain compound (69).



Then compound (69) is hydrogenated to obtain compound (70) according to the same method to prepare compound (5). Compound (70) is reacted several sulfonyl chlorides (7), sulfonic acid anhydrides (8), EtOOC·CH_2SO_2Cl or methyloxalate to obtain the compound of general formula (I).



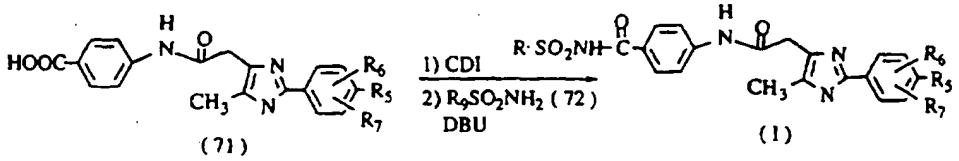
(b) In case of



in which R_3 is R_9SO_2NHCO- (R_9 = alkyl or thienyl), and R_4 is H.

As shown in the following reaction diagram,

carboxylic acid of compound (71) is reacted with CDI (Carbonyl Diimidazole) and then subjected to react with sulfamine of compound (72) in the presence of DBU (1,8-Diazabicyclo[5,4,0]undeca-7-ene) and obtain the compound of general formula (I). (Bioorg.Med.Chem. Lett.1995,1155)



As pharmaceutical acceptable salts of a compound of general formula (I), sodium salt, potassium salt and inorganic base are mentioned.

In case of R_1 contains pyridine base, salts of inorganic and organic acids are mentioned. As the salt of inorganic acid, hydrochloride and sulfate are mentioned. As the salt of organic acid, acetate, succinate and fumalate are mentioned.

A compound of general formula (I) can be used itself or formulated to pharmaceutical product such as powder, granule, tablet and capsule by known pharmaceutical technology.

PHARMACOLOGICAL EXPERIMENT

Hypoglycemic activity in mice

Test compounds were suspended in 0.5% Methyl cellulose solution and administered (p.o.) to db/db mice (obtained from Nihon Clea) at a range of 3-30mg/kg once a day for four consecutive days. Troglitazone (300mg/kg) was also administered for control. The results is shown in Table 1.

The compound number corresponds to the experimental number.

[Table 1]

Compound No.	Dosage (mg/kg)	Hypoglycemic activity (%)
1	30	24.6
2	10	49.0
8	10	26.0
9	10	24.0
10	10	32.4
11	10	15.4
18	10	34.7
19	10	12.8
21	10	34.6
24	10	25.7
26	30	15.1
30	30	22.1
31	30	19.0
35	30	28.8
40	30	53.4
42	10	29.6
47	10	25.6
48	30	65.4
50	30	21.9
52	30	10.5
57	3	44.0
58	3	43.4
59	3	18.4
63	3	18.4
67	3	33.1
68	3	21.2
70	30	51.0
Troglitazone	300	34.0

EXAMPLE

The following Examples are provided only for the purpose of the preparation of the compound and not restrict the disclosed invention.

Example 1

4-[2-(5-Methyl-2-phenyl-1,3-oxazole-4-yl)ethoxy]benzene methylsulfonamide

(a) 5-Methyl-4-tosyloxyethyl-2-phenyl-oxazole

22.2g of 5-Methyl-4-hydroxyethyl-2-phenyl-oxazole was dissolved in a mixture of pyridine (13mL) and dichloroethane (6mL) and toluenesulfonyl chloride was added slowly to the mixture and stirred at room temperature over night. The reaction mixture was poured into water and extracted with ethyl acetate (50mL) . The organic extract was washed with satd. $CuSO_4$ solution, H_2O and satd. NaCl solution. Removal of solvents after drying over anhydro. Na_2SO_4, followed by column chromatography (ethyl acetate : n-hexane = 1 : 1) yielded 3.33g (87.6%) of a white solid of the objective compound.

MASS(m/e):371(M+),216,186(BP),156,130,105,77,51

IR(cm^{-1}):1359,1173,966,927,834,813,753,666

^{1}HNMR($CDCl_3$) δ : 2.01-2.08 (m, 2H, -CH_2-), 2.29 (S, 3H, -CH_3), 2.42 (S, 3H, -CH_3), 2.55 (t, 2H, -CH_2-, J=6.83,7.33Hz), 4.08 (t, 2H, -CH_2-, J=5.86,6.34Hz), 7.31 (d, 2H, aromatic, J=7.81Hz), 7.40-7.43 (m, 3H, aromatic), 7.78 (d, 2H, aromatic, J=8.3Hz), 7.93 (dd, 2H, aromatic, J=7.33, 7.81Hz)

(b) 5-Methyl-4-p-nitrophenoxyethyl-2-phenyl-1,3-oxazole

0.21g of NaH was placed in a 50mL flask and washed twice with n-hexane and added 10mL of dimethylformamide. 0.67g of p-nitrophenol was added to the solution at 0°C and stirred for 30min. To this mixture, the compound (1.8g) obtained from the above mentioned step (a) in dimethyl formamide (5mL) was added and stirred at 80°C over night. After cooling, the reaction mixture was poured into water and the product was extracted with ethyl acetate (80mL). The ethyl acetate phase was washed with H_2O, satd. NaCl solution and dried over Na_2SO_4 and filtered. Evaporation of the filtrate gave a residue, from which 1.24g (75.6%) of the yellowish objective compound was obtained by silicagel column chromatography (ethyl acetate : n-hexane = 1 : 3). m.p.=100-103°C

MASS(m/e):338(M+),200,173(BP),130,104,77,51

IR(cm^{-1}):1590,1500,1332,1263,1107,840

^{1}HNMR($CDCl_3$) δ : 2.18-2.24 (m, 2H, -CH_2-), 2.29 (S, 3H, -CH_3), 2.71 (t, 2H, -CH_2-, J=7.33, 6.83Hz), 4.09 (t, 2H, -CH_2-, J=6.35, 5.86Hz), 6.95 (d, 2H, aromatic, J=9.28Hz), 7.41-7.44 (m, 3H, aromatic), 7.97 (dd, 2H, aromatic, J=7.32, 7.82Hz), 8.19 (d, 2H, aromatic, J=9.28Hz)

(c) 5-Methyl-4-p-aminophenoxyethyl-2-phenyl-1,3-oxazole

1.23g of the compound obtained from the above mentioned step (b) was dissolved in a solution of 25mL of methanol-tetrahydrofuran (1 : 1) and added 0.25g of 5% Pd-C. To this solution was introduced hydrogen-gas for 1 hour. After filtration of the reaction mixture, the filtrate was evaporated to give a residue, from which 1.02g (91.1%) of the objective compound was obtained by silicagel column chromatography (ethyl acetate : n-hexane = 1 : 1). m.p.=57-59°C

MASS(m/e):308(M+),200(BP),174,104,80,53

IR(cm^{-1}):1512,1242,825,711,681

^{1}HNMR($CDCl_3$) δ : 2.08-2.15 (m, 2H, -CH_2-), 2.28 (S, 3H, -CH_3), 2.68 (t, 2H, -CH_2-, J=7.33, 7.32Hz), 3.42 (bs, 2H, -NH_2), 3.90 (t, 2H, -CH_2-, J=6.35, 5.86Hz), 6.62-6.66 (m, 2H, aromatic), 6.73-6.76 (m, 2H, aromatic), 7.38-7.45 (m, 2H, aromatic), 7.96-7.99 (m, 2H, aromatic)

(d) 4-[2-(5-Methyl-2-phenyl-1,3-oxazole-4-yl)ethoxy]benzene methylsulfonamide (compound 1)

To a mixture of 0.4g of the compound obtained from the above mentioned step (c) and 0.28mL of triethylamine in dichloroethane (4mL) and 0.16mL of mesyl chloride were added and stirred at 30 °C for 30 minutes. The reaction mixture was poured into water and extracted with ethyl acetate. The ethyl acetate phase was washed with satd. NH_4Cl solution, water and satd. NaCl solution and dried over anhydrous Na_2SO_4 and filtrated. Evaporation of the filtrate gave a residue, from which 0.34g (66.7%) of the off-white objective compound was obtained by silicagel column chromatography (ethyl acetate : n-hexane = 1 : 1). m.p.=121-123°C

MASS(m/e):372(M+),264,186(BP),149,104,79,55

IR(cm^{-1}):3238,1506,1320,1281,1245,1212,1143,777

^{1}HNMR($CDCl_3$) δ : 2.38 (S, 3H, -CH_3), 2.93 (S, 3H, -SO_2CH_3), 2.98 (t, 2H, -CH_2-, J=6.35, 6.84Hz), 4.23 (t, 2H, -CH_2-, J=6.83, 6.84Hz), 6.25 (S, 1H, -NH), 6.88 (d, 2H, aromatic, J=8.79Hz), 7.16 (d, 2H, aromatic, J=9.27Hz), 7.39-7.45 (m, 3H, aromatic), 7.97 (dd, 2H, aromatic, J=1.46, 1.95Hz)

Example 2

4-[2-(5-Methyl-2-phenyl-1,3-oxazole-4-yl)ethoxy]benzene trifluoromethyl sulfonamide (compound 2)

To a mixture of the compound (0.4g) obtained from Example 1 step (c) in 4mL of dichloromethane and 0.27mL of triethylamine was added trifluoromethanesulfonic acid anhydride (3.3mL) and stirred for 30 minutes at 0°C. To the reaction mixture were added 2mL of methanol and 1mL of 10% NaOH solution and the mixture was stirred for 10 minutes, followed by addition of water (20mL) and extracted with ethyl acetate. The extract was washed with satd. NH_4Cl, water and satd. NaCl and dried over anhydrous Na_2SO_4. After filtrating, the extract was evaporated and the residue was

purified by silicagel column chromatography. Using a eluants (ethyl acetate : n-hexane = 1 : 1), 0.38g (66.7%) of the objective compound was obtained. m.p.=97-99°C

MASS(m/e):441(M+),200(BP),173,104,69

IR(cm^{-1}):1455,1248,1215,1116,894,597

^{1}HNMR($CDCl_3$) δ : 2.17-2.23 (m, 2H, -CH_2-), 2.29 (S, 3H, -CH_3), 2.70 (t, 2H, -CH_2-, J=6.83, 7.33Hz), 4.05 (t, 2H, -CH_2-, J=5.86, 6.34Hz), 6.97 (d, 2H, aromatic, J=8.79Hz), 7.40-7.44 (m, 3H, aromatic), 7.98 (dd, 2H, aromatic, J=7.32, 8.30Hz)

Example 3

5-Methyl-4-[2-(4-carboxymethylsulfonylamino)phenoxy]ethyl-2-phenyl-1,3-oxazole (compound 3)

(a) 5-Methyl-4-[2-(4-ethoxycarbonylmethyl sulfonylamino)phenoxy]ethyl-2-phenyl-oxazole

To a solution of the compound (0.36g) obtained from the above mentioned Example 1 step (c) and triethylamine (0.26mL) in dichloroethane (8mL) was slowly added ethoxy carbonyl chloride (0.27g) at 0°C and stirred for 2 hours. The reaction mixture was poured into water and the product was extracted with ethyl acetate. The extract was washed with satd. NH_4Cl, water and satd. NaCl and dried over anhydrous Na_2SO_4 and filtrated. Evaporation of the filtrate gave a residue, from which 0.32g (59.1%) of the oily objective compound was obtained by silicagel column chromatography (ethyl acetate : n-hexane = 1 : 1).

MASS(m/e):443(M+),186(BP),144,108,84,47

IR(cm^{-1}):1734,1341,1299,1248,1158,753

^{1}HNMR($CDCl_3$) δ : 1.32 (t, 3H, -COOEt, J=6.84, 7.32Hz), 2.38 (S, 3H, -CH_3), 2.98 (t, 2H, -CH_2-, J=6.83, 6.35Hz), 3.86 (S, 2H, -CH_2-), 4.23 (t, 2H, -CH_2-, J=6.83, 6.35Hz), 4.28 (q, 2H, -COOEt, J=7.32, 6.83Hz), 6.74 (S, 1H, -SO_2NH), 6.88 (d, 2H, aromatic, J=8.78Hz), 7.25 (d, 2H, aromatic, J=8.30Hz), 7.39-7.44 (m, 3H, aromatic), 7.97 (q, 2H, aromatic, J=1.46, 1.96Hz)

(b) 5-Methyl-4-[2-(4-carboxymethyl sulfonylamino)phenoxy]ethyl-2-phenyl-1,3-oxazole (compound 3)

To a solution of the compound (0.3g) obtained from the above mentioned step (a) in ethanol (5mL) was added 10% NaOH (2.5mL) and the solution was stirred for 1 hour. After removing the solvent, the residue was dissolved in water and washed with ether. After acidification with 10% HCl,the water phase was extracted with ethyl acetate. The ethyl acetate phase was washed with water, satd. NaCl and dried over anhydrous Na_2SO_4. After removing the solvent, the residue was recruptallized from ethyl acetate. 0.2g (71.4%) of the objective compound was obtained. m.p.=164-167°C

MASS(m/e):371(M+ -COOH),294,186(BP),144,104,77

IR(cm^{-1}):3274,1713,1512,1338,1281,1245,1158,1107

^{1}HNMR ($CDCl_3$) δ :2.42 (S, 3H, $-CH_3$), 3.06 (t, 2H, $-CH_2-$, J=6.35Hz), 3.86 (S, 2H, $-CH_2-$), 4.24 (t, 2H, $-CH_2-$, J=6.83, 6.35Hz), 6.85 (d, 2H, aromatic, J=9.28Hz), 7.22 (d, 2H, aromatic, J=8.78Hz), 7.45-7.47 (m, 3H, aromatic), 7.95 (q, 2H, aromatic, J=2.44, 3.9Hz)

Example 4-5

According to the method described in Example 3, compound 4 (oil), compound 5 (m.p.=273-239°C), compound 6 (m.p.=143-145°C) and compound 7 (m.p.=114-116°C) were obtained.

Example 8

2-[4-(2-(5-Methyl-2-phenyl-1,3-oxazole-4-yl)ethoxy)phenyl]amino-2-oxo-acetic acid (compound 8)

(a) 2-[4-(2-(5-Methyl-2-phenyl-1,3-oxazole-4-yl)ethoxy)phenyl]amino-2-oxo-acetic acid methyl aster

A mixture of the compound (0.5g) obtained from the above mentioned Example 1 step (c) and methyl oxalate (0.6g) in methanol (10mL) was refluxed over night. After cooling, the solvent was evaporated and a resulting residue was purified by silicagel column chromatography. Chloroform was used as a eluant. 0.55g (84.6%) of the objective compound was obtained. m.p.=128-132

MASS(m/e):380(M+),321,186(BP),144,105,59

^{1}HNMR($CDCl_3$) δ : 2.37 (S, 3H, $-CH_3$), 2.98 (t, 2H, $-CH_2-$, J=6.84, 6.35Hz), 3.96 (S, 3H, -COOMe), 4.24 (t, 2H, $-CH_2-$, J=6.35, 6.83Hz), 6.90 (d, 2H, aromatic, J=8.79Hz), 7.38-7.44 (m, 3H, aromatic), 7.53 (d, 2H, aromatic, J=8.79Hz), 7.97 (d, 2H, aromatic, J=5.86Hz), 8.76 (d, S, 1H, -NH)

(b) 2-[4-(2-(5-Methyl-2-phenyl-1,3-oxazole-4-yl)ethoxy)phenyl]amino-2-oxo-acetic acid (compound 8)

A mixture of the compound (0.53g) obtained from the above mentioned Example 8 step (a) and 10% NaOH in methanol (15mL) was stirred for 1 hour and water (30mL) was added to the mixture, followed by acidification (pH 4) with 10% HCl to give a crptalline product. Recrystallization from ethyl acetate gave the objective compound (0.42g, 82.3%). m.p.=196-198 °C

MASS(m/e):366(M+),322,294,186(BP),144,104,77

^{1}HNMR($CDCl_3$) δ : 2.36 (S, 3H, $-CH_3$), 2.92 (t, 2H, $-CH_2-$, J=6.35, 6.83Hz), 3.32 (bs, 1H, -NH), 4.19 (t, 2H, $-CH_2-$, J=6.34, 6.84Hz), 6.93 (d, 2H, aromatic, J=9.27Hz), 7.45-7.55 (m, 3H, aromatic), 7.67 (dd, 2H, aromatic, J=2.44Hz), 7.91 (dd, 2H, aromatic, J=1.47, 1.95Hz)

Example 9

2-[4-(2-(5-Methyl-2-phenyl-1,3-oxazole-4-yl)ethoxy)benzyl]trifluoromethylsulfonamide

(compound 9)

(a) 5-Methyl-4-(2-p-benzylaminophenoxy)-ethyl-2-phenyl-1,3-oxazole

A mixture of 5-methyl-4-[2-(p-formylphenoxy)]ethyl-2-phenyl-1,3-oxazole (0.54g) and benzylamine (0.21mL) in methanol (10mL) was stirred for 10 minutes and $NaBH_3CN$ (0.11g) was added to the mixture. The mixture was stirred over night and evaporated and to a resulting residue was added 10% HCl with stirring, followed by addition of satd. $NaHCO_3$ to alkalize. The product was extracted with ethyl acetate. The ethyl acetate phase was washed with H_2O, satd. NaCl and dried over anhydrous Na_2SO_4 and filtered. Evaporation of the filtrate gave a residue, from which 0.43 (61.4%) of the oily objective product was obtained by silicagel column chromatography.

MASS(m/e):398(M+),291,212,186(BP),146,104,77

IR(cm^{-1}):3022,2914,1608,1509,1452,1242,738,714

^{1}HNMR($CDCl_3$) δ : 2.37 (S, 3H, $-CH_3$), 2.98 (t, 2H, $-CH_2-$, J=6.83, 6.84Hz), 3.73 (S, 2H, $-CH_2-$), 3.78 (S, 2H, $-CH_2-$), 4.24 (t, 2H, $-CH_2-$, J=6.84, 6.83Hz), 6.86 (d, 2H, aromatic, J=8.79Hz), 7.21-7.44 (m, 10H, aromatic), 7.97 (q, 2H, aromatic, J=1.46, 1.95Hz)

(b) 5-Methyl-4-(2-p-aminophenoxy)ethyl-2-phenyl-1,3-oxazole

The compound (0.4g) obtained from the above mentioned Example 9 step (a) was dissolved in methanol (10mL) containing a small amount of HOAc and 5% Pd-C (80mg). The mixture is hydrogenated and the reaction mixture was filtered and the filtrate was evaporated. A resulting residue was purified by silicagel column chromatography using a eluant ($CHCl_3$: MeOH = 10 : 1). The objective compound (0.21g, 67.7%) was obtained. m.p.=149-152°C

MASS(m/e):308(M+),291,186(BP),144,122,104,77

IR(cm^{-1}):3430,2962,1608,1248

^{1}HNMR($CDCl_3$) δ : 3.88 (S, 2H, $-CH_2-$), 4.23 (t, 2H, $-CH_2-$, J=6.34, 6.84Hz), 6.90 (d, 2H, aromatic, J=8.79Hz), 7.27 (d, 2H, aromatic, J=8.78Hz), 7.41-7.46 (m, 3H, aromatic), 7.96 (d, 2H, aromatic, J=7.81Hz)

(c) 2-[4-(2-(5-Methyl-2-phenyl-1,3-oxazole-4-yl)ethoxy)benzyl]trifluoromethyl sulfonamide (compound 9)

The compound (0.14g) obtained from the above mentioned Example 9 step (b) was reacted with trifluoromethanesulfonamide as same manner as Example 2 and the objective compound (compound 9) was obtained (0.55g, 28%). m.p.=113-115°C

MASS(m/e):440(M+),186,144,104(BP),77

IR(cm^{-1}):3310,1443,1368,1251,1227,1188,1146

^{1}HNMR($CDCl_3$) δ : 2.38 (S, 3H, $-CH_3$), 2.98 (t, 2H, $-CH_2-$, J=6.83, 6.84Hz), 4.25 (t, 2H, $-CH_2-$, J=6.84, 6.34Hz), 4.37 (d, 2H, $-CH_2-$, J=4.89Hz), 5.05 (bs, 1H, $-NHSO_2-$), 6.90 (d, 2H, aromatic,

J=8.79Hz), 7.22 (d, 2H, aromatic, J=8.79Hz), 7.41-7.45 (m, 3H, aromatic), 7.97 (q, 2H, aromatic, J=1.95, 1.96Hz)

Example 10

4-[2-(5-Ethylpyridine-2-yl)ethoxy]benzene trifluoromethylsulfonamide (compound 10)

(a) 2-[2-(4-Nitrophenoxy)]ethyl-5-ethyl-pyridine

To a mixture of 2-(5-ethylpyridine) ethanol (10g) and 4-fluoronitrobenzene (9.3g) in Dimethylformamide (100mL) was added NaOH (3.4g) and the mixture was stirred at 0°C for 1 hour. After pouring into ice-water, the product was extracted with ethyl acetate (150mL). The ethyl acetate phase was washed with satd. NaCl and dried over anhydrous Na_2SO_4. After removing the solvent, the resulting residue was purified by silicagel column chromatography (EtoAc : n-hexane = 1 : 2 → 2 : 1). Recrystallization from EtoAc n-hexane mixture (1 : 1) gave the off-white objective compound. 13.4g (74.4%), m.p.=45-47°C

MASS(m/e):272(M+),150,134(BP),119,93,77

IR(cm^{-1}):1593,1518,1491,1341,1260,1008,834

^{1}HNMR($CDCl_3$) δ : 1.25 (t, 3H, -C_2H_5, J=7.81, 7.32Hz), 2.64 (q, 2H, -C_2H_5, J=7.33, 7.32Hz), 3.27 (t, 2H, -CH_2-, J=6.34, 6.84Hz), 4.46 (t, 2H, -CH_2-, J=6.34, 6.84Hz), 7.17 (d, 1H, pyridine, J=8.31Hz), 7.47 (dd, 1H, pyridine, J=2.44, 2.45Hz), 8.18 (dd, 2H, aromatic, J=6.83, 7.32Hz), 8.40 (d, 1H, pyridine, J=1.95Hz)

(b) 2-[2-(4-Aminophenoxy)]ethyl-5-ethyl-pyridine

The compound (1.85g) obtained from the above mentioned Example 10 step (a) was hydrogenated as same manner as Example 1 step (c) and obtained the oily objective compound (1.62g, 98.2%).

MASS(m/e):242(M+),134(BP),119,106,83,65

IR(cm^{-1}):2950,1509,1233,822

^{1}HNMR($CDCl_3$) δ : 1.24 (t, 3H, -C_2H_5, J=7.81, 7.33Hz), 2.62 (q, 2H, -C_2H_5, J=7.33Hz), 3.19 (t, 2H, -CH_2-, J=6.35, 6.83Hz), 3.42 (bs, 2H, -NH_2), 4.26 (t, 2H, -CH_2-, J=6.35, 6.84Hz), 6.61-6.64 (m, 2H, aromatic), 6.72-6.76 (m, 2H, aromatic), 7.18 (d, 1H, pyridine, J=7.81Hz), 7.44 (dd, 1H, pyridine, J=1.95, 1.96Hz), 8.39 (d, 1H, pyridine, J=2.46Hz)

(c) 4-[2-(5-Ethylpyridine-2-yl)ethoxy]benzene trifluoromethylsulfonamide (compound 10)

The compound (1.2g) obtained from the above mentioned Example 10 step (b) was reacted with trifluoromethanesulfonic acid anhydride by the same procedure described in Example 2 and obtained 0.3g the objective compound (compound 10). m.p.=76-78°C

MASS(m/e):373(M+ -1),134(BP),91,69

IR(cm^{-1}):1446,1263,1119,897,603

^{1}HNMR($CDCl_3$) δ : 1.25(t, 3H, -C_2H_5, J=7.81, 7.33Hz), 2.63 (q, 2H, -C_2H_5, J=7.32, 7.82Hz), 3.25 (t, 2H, -CH_2-, J=6.83, 6.35Hz), 4.39 (t, 2H, -CH_2-, J=6.35Hz), 6.96 (dd, 2H, aromatic, J=6.84, 6.83Hz), 7.18 (d, 1H, pyridine, J=7.81Hz), 7.28 (d, 2H, aromatic, J=9.28Hz), 7.46 (dd, 1H, pyridine, J=7.81Hz), 8.40 (d, 1H, pyridine, J=1.96Hz)

Example 11

4-[2-(N-Methyl-N-2-pyridyl)aminoethoxy]benzene trifluoromethanesulonamide (compound 11)

(a) 4-[2-(N-Methyl-N-2-pyridyl)aminoethoxy]-1-nitrobenzene-2-pyridyl-2-methylamino ethanol (4.0g) was reacted with 4-fluorobenzene by the same procedure described in Example 6 step (a) and obtained the oily objective compound (5.9g, 82.2%).

MASS(m/e):273(M+),139,121(BP),94,78,51

IR(cm^{-1}):2926,1590,1497,1425,1338,1260

^{1}HNMR($CDCl_3$) δ : 3.14 (S, 3H, -CH_3), 4.03 (t, 2H, -CH_2, J=5.86, 5.37Hz), 4.30 (t, 2H, -CH_2-, J=5.86Hz), 5.52 (d, 1H, pyridine, J=8.79Hz), 6.59 (t, 1H, pyridine, J=4.88, 6.35Hz), 6.97 (dd, 2H, aromatic, J=8.79Hz), 7.45-7.50 (m, 1H, pyridine), 8.15-8.20 (m, 2H, pyridine, aromatic)

(b) 4-[2-(N-Methyl-N-2-pyridyl)aminoethoxy]-1-aminobenzene

The compound (5.85g) obtained from the above mentioned Example 11 step (a) was hydrogenated by the same procedure described in Example 1 step (c) and obtained the objective compound (2.12g, 40.7%).

MASS(m/e):243(M+),135(BP),121,108,94,78,65

IR(cm^{-1}):3334,2914,1596,1557,1503,1425,1233,771

(c) 4-[2-(N-Methyl-N-2-pyridyl)aminoethoxy]benzene trifluoromethanesulfonamide (compound 11)

The compound (0.5g) obtained from the above mentioned Example 11 step (b) was reacted with trifluoromethanesulfonamide by the same procedure described in Example 2 and obtained the objective product (0.67g, 87.0%). m.p.=60-62°C

MASS(m/e):375(M+),304,170,135,108,78(BP),52

IR(cm^{-1}):1593,1503,1452,1218,1125,891,600

^{1}HNMR($CDCl_3$) δ : 3.13 (S, 3H, -CH_3), 4.01 (t, 2H, -CH_2, J=5.86, 5.37Hz), 4.24 (t, 2H, -CH_2-, J=5.86, 5.37Hz), 6.51 (d, 1H, pyridine, J=8.30Hz), 6.57 (t, 1H, pyridine, J=4.88, 6.84Hz), 6.97 (d, 2H, aromatic, J=9.27Hz), 7.27 (d, 2H, aromatic, J=9.77Hz), 7.44-7.49 (m, 1H, pyridine), 8.15 (d, 1H, pyridine, J=3.90Hz)

Example 12-17

According to the method described in Example 1, compound 12 (m.p.=106-108°C), compound 13(m.p.=67-68°C), compound 14 (m.p.=56-58°C), compound 15 (m.p.=128-130°C), compound 16 (126-127°C) and compound 17 (m.p.=128-130°C) were obtained.

Example 18-20

According to the method described in Example 2, compound 18 (m.p.=197-198°C), compound 19 (m.p.=70-71°C) and compound 20 (m.p.=170-172°C) were obtained.

Example 21

5-Methyl-4-(3-hydroxy)propyl-2-phenyl-1,3-oxazole, prepared from glutamic acid instead of asparatic acid, was reacted as a similar manner described in Experimental 2 and obtained compound 21 (m.p.=113-114°C).

Example 22-24

According to the same procedure described in Example 4, compound 22 (m.p.=128-130°C) and compound 23 (m.p.=217°C (decomp.)) were obtained.

Example 25

2-Hydroxy-4-[2-(5-methyl-2-phenyl-1,3-oxazole-4-yl)ethoxy]benzoic acid methyl ester (compound 25)

0.2g of methyl 2-4-dihydroxybenzoate and 0.23g of diisopropyl azodicarboxylate (DIAD) were dissolved in 2mL of THF. To this mixture was slowly added a mixture of 0.29g of 5-methyl -4-hydroxyethyl-3-phenyl-1,3-oxazole and 0.31g of Ph_3P in 3mL of THF and the mixture was subjected to Mitsunobu reaction. After the reaction mixture was allowed to stand over night, the solvent was removed. The resulting residue was purified by silicagel column chromatography (ethyl acetate : benzene = 1 : 5). After removing the solvent, the residue was recrystallized from benzene. 0.31g (73.3%) of the colorless objective compound was obtained. m.p.=133-134°C

MASS(m/e):353(M+),217,185,136,104(BP),77,53

IR(cm^{-1}):1677,1617,1440,1320,1251,1188,1134

^{1}HNMR($CDCl_3$) δ : 3.90 (S, 3H, -COOMe), 4.27 (t, 2H, $-CH_2$, J=6.34, 6.84Hz), 6.42 (dd, 1H, -aromatic, J=8.79Hz), 6.46 (d, 1H, aromatic, J=2.44Hz), 7.39-7.44 (m, 3H, aromatic), 7.72 (d, 1H, aromatic, J=9.28Hz), 7.97 (q, 2H, aromatic, J=7.33, 8.3Hz), 10.93 (s, 1H, -OH)

Example 26-28

According to the procedure described in Example 11, compound 26 (m.p.=211-213°C),

compound27 (m.p.=85-87°C) and compound 28 (m.p.=130-132°C) were obtained.

Example 29-30

2-Hydroxy-4-[2-(5-methyl-2-phenyl-1,3-oxazole-4-yl)ethoxy]benzoic acid (compound 29)

0.17g of the compound obtained from Example 20 was dissolved in 2mL of MeOH : THF (1 : 1). To the solution was added 2mL of 10% NaOH and the mixture was refluxed for 1 hour. After removal of the solvent, the residue was washed with ether, followed by acidification with 10% HCl. The resulting precipitate was filtered. Recrystallization from ethanol gave the colorless objective compound (0.13g, 81.3%). m.p.=192-194°C

MASS(m/e):339(M+),295,217,186,104(BP)

IR(cm^{-1}):2920,1655,1260,1170

According to the above mentioned procedure compound 30 was obtained. (m.p.=246-266°C).

Example 31-32

2-Ethoxy-4-[2-(5-methyl-2-phenyl-1,3-oxazole-4-yl)ethoxy]benzoic acid (compound 31)

(a) 2-Ethoxy-4-[2-(5-methyl-2-phenyl-1,3-oxazole-4-yl)ethoxy]benzoic acid methyl ester

To a solution of the compound 25 (0.27g) in DMF (5mL) was added K_2CO_3 (0.16g) and EtI (0.07mL) and the mixture was allowed to stand over night. The reaction mixture was poured into water and the product was extracted with ethyl acetate (30mL). The ethyl acetate phase was washed with water, satd. NaCl and dried over anhydrous Na_2SO_4 and filtrated. Evaporation of the filtered gave a residue, from which 0.28g (96.6%) of the colorless objective compound was obtained by silicagel column chromatography (ethyl acetate : n-hexane = 1 : 3).

MASS(m/e):381(M+),217,186,144,104(BP),77,51

IR(cm^{-1}):2926,1686,1605,1257,1194

(b) 2-Ethoxy-4-[2-(5-methyl-2-phenyl-1,3-oxazole-4-yl)ethoxy]benzoic acid (compound 31)

The compound obtained from above mentioned Example 31-32 step (a) was hydrolyzed by the procedure in Example 29 and obtained the objective compound (0.22g). m.p.=128-130°C

MASS(m/e):367(M+),217,186,144,104(BP),77,51

IR(cm^{-1}):1686,1605,1572,1281,1263,1239,1191

^{1}HNMR($CDCl_3$) δ : 2.99 (t, 2H, -CH_2-, J=6.84Hz), 4.25 (q, 2H, oEt, J=6.84Hz), 4.33 (t, 2H, -CH_2-, J=6.34, 6.84Hz), 6.50 (d, 1H, aromatic, J=2.44Hz), 6.55 (dd, 1H, aromatic, J=1.95Hz), 7.41-7.44 (m, 3H, aromatic), 7.96-7.99 (m, 2H, aromatic), 8.10 (d, 1H, aromatic, J=8.79Hz)

And compound 25 was reacted with methoxy methylchloride to obtain compound 32. m.p.=129-130°C.

Example 33-38

Each compounds of 3-benzyl-4-nitrophenol-2,6-difluoro-4-nitrophenol and 5-methyl-4-hydroxyethyl-2-phenyl-1,3-oxazole were subjected to Mitsunobu reaction in a similar manner described in Example 25 and the nitro compounds were obtained, followed by the procedures described in Example 1 step (c) and step (d) yielded compound 33 (m.p.=155-156°C), compound35 (m.p.=143-144°C) and compound 36 (m.p.=78-80°C). Further, Mitsunobu reaction of 2,4-dihydroxy-benzene sulfonamide and 5-methyl-4-hydroxy-3-phenyl-1,3-oxazole yielded compound 34 (m.p.=231-232°C). Ethylation of the compound 34 yielded compound 37 (m.p.=171-173°C). Methyl 4-hydroxy -2-ethoxyphenoxy acetate was reacted in a similar manner and the resulting compound was hydrolyzed to obtain compound 38 (m.p.=154-156°C).

Example 39

4-[2-(N-Methyl-N-2-pyridyl)aminoethoxy]-2-hydroxyphenyl trifluoromethane sulfonamide (compound 39)

(a) 4-[2-(N-Methyl-2-N-pyridyl)aminoethoxy]-2-hydroxy nitrobenzene.

To a mixture of 2-(N-methyl, N-hydroxyethyl)-aminopyridine (0.35g) and 4-fluoro-2-methoxy-methyloxy-nitrobenzene in DMF (30mL) was added NaH (0.12g) and stirred at room temperature over night. The reaction mixture was poured into ice-water and extracted with ethyl acetate. The ethyl acetate extract was washed with satd. NHCl and dried over anhyd. Na_2SO_4 and filtered. After removal of solvent, the residue was purified by silicagel column chromatography (ethyl acetate : n-hexane = 1 : 2). The oily objective compound (0.44g, 57.1%) was obtained.

MASS(m/e):333(M+),121(BP),78,52

IR(cm^{-1}):2926,1596,1500,1425,1341,1287,1152

(b) 4-[2-(N-Methyl-N-2-pyridyl)aminoethoxy]-2-hydroxyphenyl trifluoromethanesulfonamide (compound 33)

The compound obtained from the above mentioned step (a) was reduced with hydrogen in a similar manner described in Example 1 step (c) and the resulting compound was reacted with trifluoromethanesulfonic acid anhydride in a similar manner described in Experimental 1 step (d). After removing of the protection group (MOM, methoxymethyl), the residue was recrystallized from the mixture of ethyl acetate and n-hexane to obtain the colorless objective compound (compound 33).

mp-134-135°C

MASS(m/e):391(M+),135(BP),107,78

IR(cm^{-1}):1611,1509,1419,1404,1227,1176,1146

^{1}HNMR($CDCl_3$) δ : 3.14 (S, 3H, Me), 3.93 (t, 2H, -CH_2, J=5.37Hz), 4.11 (2H, -CH_2-, J=5.37Hz), 6.37-6.43, 6.53-6.59 (m, m, 4H, aromatic, pyridine), 7.27 (d, 1H, aromatic,

J=8.79Hz), 7.46-7.51 (m, 1H, pyridine), 8.08 (d, 1H, pyridine, J=4.88Hz)

Example 40-41

Compound 40 (m.p.=133-135°C) and compound 41(m.p.=151-153°C) were obtain from 4-fluoro-2-ethoxy-nitrobenzene by proceeding in a similar manner described in Experimental 39 step (a).

Example 42-45

In stead of 2-(N-Methyl, N-hydroxyethyl) aminopyridine in Example 39 step (a), 5-methyl-4-hydroxy-2-phenyl-1,3-oxazole was reacted in a similar manner and the resulting compound was reacted with trifluoromethanesulfonic acid anhydride to obtain compound 43 (m.p.=169-171°C). The compound obtained from Example 39 step (a) was reacted with trifluoromethanesulfonic acid anhydride to obtain compound 44 (m.p.=124-125°C). Further, 2-(N-Methyl, N-hydroxyethyl)-amino pyridine in Example 39 step (a) was reacted with 4-fluoro-2-methoxy-nitrobenzene and the resulting product was treated with in a similar manner described in Example 1 step (c) to obtain the oily objective compound 45.

Example 46-47

N-Butyl-2,4-dihydroxy-benzenesulfonamide and 5-methyl-4-bromoethyl-2-phenyl-1,3-oxazole was reacted in a similar manner described in Example 1 step (b) to obtain compound 46 (m.p.=137-139°C). After reacting 2,6-dibromo-4-hydroxy-benzoic acid methyl ester and 5-methyl-4-bromoetyl-2-phenyl-1,3-oxazole, compound 47 (m.p.=163-164°C) was obtained.

Example 48-54

After chlorination of the compound of general formula (68), the resulting compound was reacted with 4-nitroaniline or corresponding aniline to obtain the compound of general formula (69), followed by reduction in a similar manner described in Example 1 and the resulting compounds were treated in a similar manner described in Example 2. The following objective compounds were obtained. Compound 53 was hydrolyzed to obtain compound 54. Compound 48 (m.p.=147-149°C), compound 49 (m.p.=175-177°C), compound 50 (m.p=166-168°C), compound 51 (m.p.=164-166°C), compound 52 (m.p.=227-229°C), compound 53 (oil), compound 54 (175°C, decomp.)

Example 55-56

After activation of carboxylic acid group in general formula (71) by the reported method (Bioorg.Med.Chem.Lett.,1995,1155), the resulting compound was reacted with sulfamines in the presence of DBU to obtain compound 55 (m.p.=150-152°C) and compound 56 (m.p.=214-216°C).

Example 57-59

In stead of 5-methyl-4-p-aminophenoxy-2-phenyl-1,3-oxazole in Example 2 , 5-methyl-4-p-aminophenoxyethyl-2-p-tolyl-1,3-oxazole, 5-methyl-4-p-aminophenoxyethyl-2-p-chlorophenyl-1,3-oxazole and 5-methyl-4-p-aminophenoxyethyl-2-p-fluorophenyl-1,3-oxazole were reacted in a similar manner described in Example 2 to obtain the following compounds. Compound 57 (m.p.=173.5-175°C), compound 58 (m.p.=189-190°C), compound 59 (m.p.=161-163°C).

Example 60-63

In stead of 5-methyl-4-p-aminophenoxy-2-phenyl-1,3-oxazole, 5-isopropyl-4-p-aminophenoxyethyl-2-p-tolyl-1,3-oxazole, 5-isopropyl-4-p-aminophenoxy-2-phenyl-1,3-oxazole, 5-isopropyl-4-p-aminophenoxyethyl-2-p-fluorophenyl-1,3-oxazole and 5-isopropyl-4-p-aminophenoxy-2-(3,5-di-*t*-butyl-4-hydroxy)phenyl-1,3-oxazole were reacted in a similar manner described in Example 2 to obtain the following compounds. Compound 60 (m.p.=190-191°C), compound 61 (m.p.=155-156°C), compound 62 (m.p.=189-190°C), compound 63 (m.p.=142-144°C).

Example 64-66

5-Isopropyl-4-hydroxyethyl-2-phenyl-1,3-oxazole, 5-isopropyl-4-hydroxyethyl-2-p-phenyl-1,3-oxazole and 5-isopropyl-4-hydroxyethyl-2-p-tolyl-1,3-oxazole were reacted with 4-fluoro-2-ethoxy-nitrobenzene in a similar manner described in Example 39 to obtain the following compounds. Compound 64 (m.p.=142-144°C), compound 65 (m.p.=179-181°C), Compound 66 (m.p.=122-124°C)

Example 67-68

Each of 5-methyl-4-hydroxyethyl-2-(p-ethoxycarbonylmethyloxy)phenyl-1,3-oxazole and 5-methyl-4-hydroxyethyl-2-(3,5-di-*t*-butyl-4-ethoxycarbonylmethyloxy)phenyl-1,3-oxazole were transformed to 5-methyl-4-p-nitrophenyl -2-(p-ethoxycarbonylmethyloxy)phenyl-1,3-oxazole and 5-methyl-4-p-nitrophenyl-2-(3,5-di-*t*-butyl-4-ethoxycarbomethyloxy)phenyl-1,3-oxazole using a similar method described in Example 39. The resulting compounds were hydrolyzed with 10% NaOH-MeOH to obtain the following compounds. Compound 67 (m.p.=167-168°C), compound 68 (m.p.=196-198°C)

Example 69

5-Methyl-4-p-formylphenyl-2-phenyl-1,3-oxazole (1.0g) was dissolved in dichlolomethane (10mL) and hydroxylamine-o-sulfonic acid (0.59g) was added. The mixture was stirred for 30 minutes and the resulting precipitate was collected, followed by washing with water, MeOH and

dichloromethane. 1.03g of compound 69 was obtained. m.p.=165-167°C
MASS(m/e):403(M+1),401(M-1)

Example70

According to a similar procedure, described in Example 2, 5-methyl-4-aminophenoxyethyl-2-(3-*t*-butyl-4-hydroxy)phenyl-1,3-oxazole were transformed to compound 70. m.p.=58-60°C.

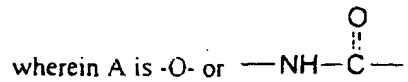
Effects of the Invention

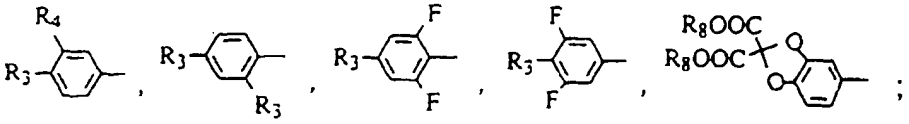
This invention concerns to novel ether and/or amide derivatives which enhance insulin action and show hypoglycemic activities with low toxicities and useful for antidiabetics.

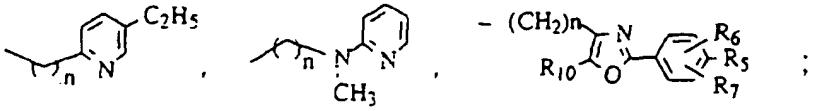
CLAIMS

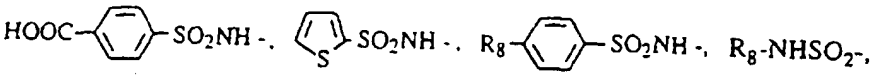
1. A compound of formula (I).

$$R_1\text{-}A\text{-}R_2 \qquad (I)$$

wherein A is -O- or 

R_1 is  ;

R_2 is  ;

R_3 is OH-, CH_3SO_2NH-, CF_3SO_2NH-, $CH_3SO_2NHCH_2$-, $CF_3SO_2NHCH_2$-, HOOC-, CH_3OOC-, R_8-OOC-C(=O)-NH-, HOOC-CH_2SO_2NH-, CF_3-CH_2SO_2NH-,  ,

R_8-$NHSO_2$-CH_2-, HOOC-CH_2-O-, HSO_3N=CH-, or R_9-SO_2NHCO-,

R_4 is H, OH, O-alkyl or O-CH_2OCH_3;

R_5 is H, halogen, -CH_2COOH or OH;

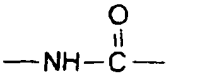
R_6 and R_7 are halogen, t-butyl or pyrrolidyl.

R_8 is hydrogen or lower alkyl;

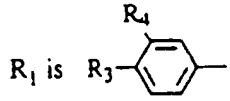
R_9 is alkyl or thienyl;

R_{10} is lower alkyl.

or a pharmaceutically acceptable salt thereof,

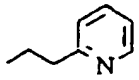
with the provisos that (i) when A is -O-, then n is 2 or 3, and (ii) when A is  , then n is 1 or 2.

2. A compound according to claim 1, wherein

R_1 is 

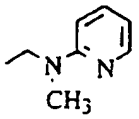
in which R_3 and R_4 are as defined above, or a pharmaceutically acceptable salt thereof.

3. A compound according to claim 1, wherein

R_2 is 

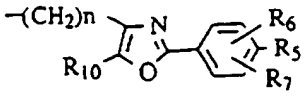
or a pharmaceutically acceptable salt thereof.

4. A compound according to claim 1, wherein

R_2 is 

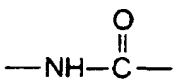
or a pharmaceutically acceptable salt thereof.

5. A compound according to claim 1, wherein

R_2 is  ;

R_5 is H or OH; R_6 and R_7 is H or t-butyl and R_{10} is lower alkyl, or a pharmaceutically acceptable salt thereof,

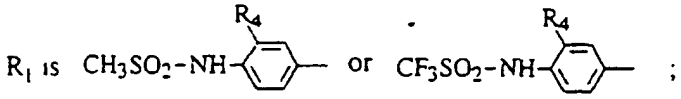
with the provisos that (i) when A is -O- then n is 2 or 3, and (ii) when A is

 then n is 1 or 2.

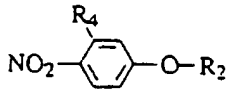
6. A pharmaceutical composition comprising a compound or salt according to any of claims 1 to 5 together with a pharmaceutically acceptable carrier or diluent.

7. A pharmaceutical composition according to claim 6, for use an antidiabetic.

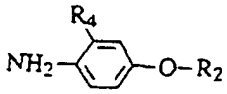
8. A process for the preparation of a compound of formula (I) as defined in claim 1, wherein A is -O-:

R_1 is  ;

and R_4 is as defined above, which process comprises reducing a compound of the following formula



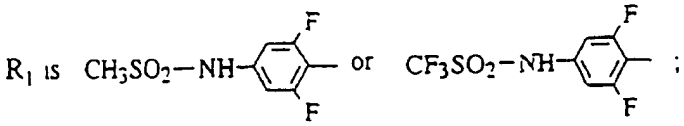
in which R_2 and R_4 are as defined above to obtain a compound of the following formula



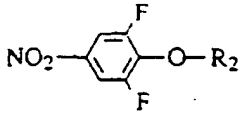
and reacting this compound with CH_3SO_2Cl or CF_3SO_2Cl to obtain the compound of formula (I).

9. A process for the preparation of a compound of formula (I) as defined in claim 1, wherein

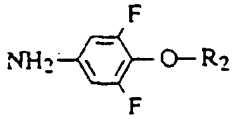
A is -O- and

R_1 is  ;

which process comprises reducing a compound of the following formula

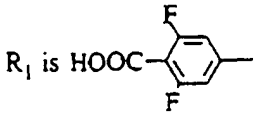


in which R_2 is as defined above, to obtain a compound of the following formula:

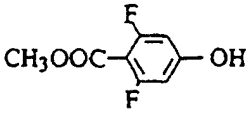


and reacting this compound with CH_3SO_2Cl or CF_3SO_2Cl to obtain the compound of formula (I).

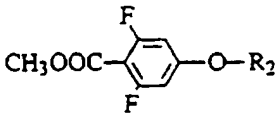
10. A process for the preparation of a compound of formula (I) as defined in claim 1, wherein A is -O-; R_2 is as defined above and



which process comprises reacting a compound of the following formula;

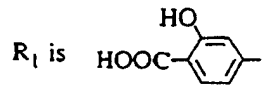


with $X\text{-}R_2$ in which X is Br, tosyl or mesyl and R_2 is as defined above, to obtain a compound of the following formula;

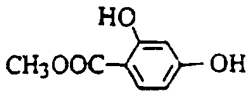


and hydrolysing this compound to obtain the compound of formula (I).

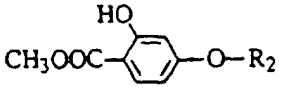
11. A process for the preparation of a compound of formula (I) as defined in claim 1, wherein A is -O-; R_2 is as defined above and



which process comprises reacting a compound of the following formula

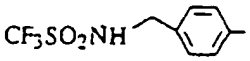


with $HO\text{-}R_2$ to obtain a compound of the following formula;

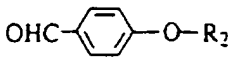


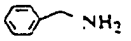
and hydrolysing this compound to obtain the compound of formula (I).

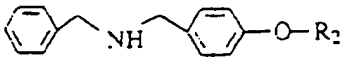
12. A process for the preparation of a compound of formula (I) as defined in claim 1, wherein A is -O-; R_2 is as defined above, and

R_1 is  or 

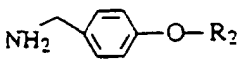
which process comprises reacting a compound of the following formula:



with  to obtain a compound of the following formula.

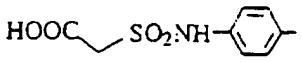


which after debenzylation, is covered to a compound of the following formula;

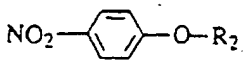


which compound is reacted with CH_3SO_2Cl or CF_3SO_2Cl to obtain the compound of formula (I).

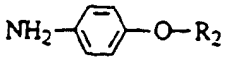
13. A process for the preparation of a compound of formula (I) as defined in claim 1, wherein A is -O-; R_2 is as defined above and

R_1 is 

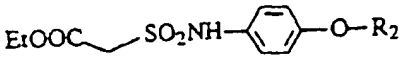
which process comprises reducing a compound of the following formula;



to obtain a compound of the following formula;

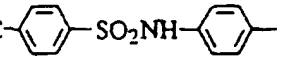


then reacting this compound with $EtOOC\text{-}CH_2\text{-}SO_2Cl$ to obtain a compound of the following formula;

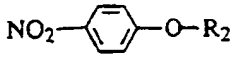


and hydrolysing this compound to obtain the compound of formula (I).

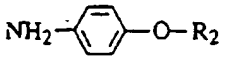
14. A process for the preparation of a compound of formula (I) as defined in claim 1, A is -O-; R_2 is as defined above, and

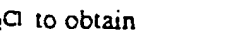
R_1 is 

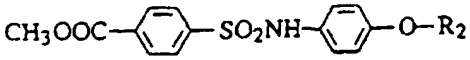
which process comprises reducing a compound of the following formula;



to obtain a compound of the following formula;

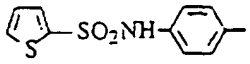
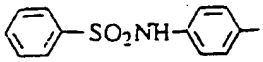


and then reacting this compound with  to obtain

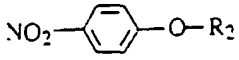


and then hydrolysing this compound to obtain a compound of general formula (I).

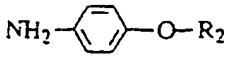
15. A process for the preparation of a compound of formula (I) as defined in claim 1, wherein A is -O-; R_2 is as defined above, and

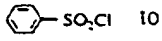
R_1 is  or 

which process comprises reducing a compound of the following formula;

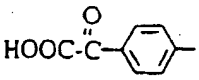


to obtain a compound of the following formula:

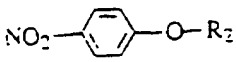


and then reacting the compound with  or  to obtain a compound of formula (I).

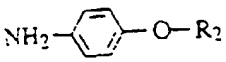
16. A process for the preparation of a compound of formula (I) as defined in claim 1, wherein A is -O-; R_2 is as defined above, and

R_1 is 

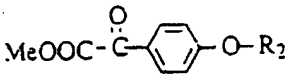
which process comprises reducing a compound of the following formula;



to obtain a compound of the following formula;

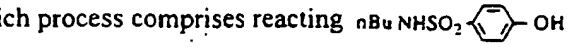


and then reacting this compound with methyloxalate to obtain a compound of the following formula;

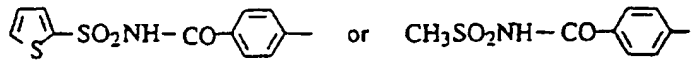


and hydrolysing this compound to obtain a compound of general formula (I).

17. A process for the preparation of a compound of formula (I) as defined in claim 1. wherein A is -O-; R_2 is as defined above, and

which process comprises reacting 
with HO-R_2 in the presence of NaH to obtain a compound of formula (I).

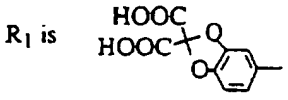
18. A process for the preparation of a compound of formula (I) as defined in claim 1, wherein A is -O-; R_2 is as defined above, and

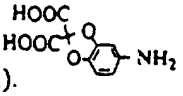


which process comprises reacting a compound of the following formula;

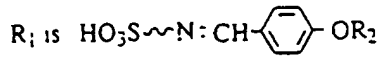
with thienyl sulfonamide or methyl sulfonamide in the presence of 1, 8-diazabicyclo[5,4,0]undeca-7-ene to obtain a compound of formula (I).

19. A process for the preparation of a compound of formula (I) as defined in claim 1, wherein A is -O-; R_2 is as defined above, and

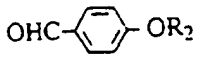


which process comprises reacting  with HOOC-R_2
to obtain a compound of formula (I).

20. A process for the preparation of a compound of formula (I) as defined in claim 1, wherein A is -O-; R_2 is as defined above, and

R_1 is 

which process comprises reacting a compound of the following formula:



with H_2NOSO_3H to obtain a compound of formula (I).

21. A compound or salt according to any of claims 1 to 5, for use as an antidiabetic.

22. Use of a compound or salt according to any of claims 1 to 5, in the manufacture of a medicament for use as an antidiabetic.

23. A compound or salt according to any of claims 1 to 5, substantially as herein described.

24. A pharmaceutical composition according to claims 6 or 7, substantially as herein described.

25. A process according to any of claims 8 to 20, substantially as herein described.

26. A compound produced by a process according to any of claims 8 to 20

Application No: GB 0100433.2
Claims searched: 1-26

Examiner: Dr William Thomson
Date of search: 7 June 2001

Patents Act 1977
Search Report under Section 17

Databases searched:

UK Patent Office collections, including GB, EP, WO & US patent specifications, in:

UK Cl (Ed.S):

Int Cl (Ed.7):

Other: ONLINE: CAS-ONLINE

Documents considered to be relevant:

Category	Identity of document and relevant passage		Relevant to claims
A, E	WO 01/16119A1	(ELI LILLY & CO) See whole document, in particular page 35, lines 15-17	
A, E	WO 01/16111A1	(ELI LILLY & CO) See whole document, in particular Scheme 3	
X	WO 96/13264A1	(ELI LILLY & CO) See whole document, in particular page 23, lines 15-22 and page 26, line 7-21	1 and 2 at least

X	Document indicating lack of novelty or inventive step	A	Document indicating technological background and/or state of the art.
Y	Document indicating lack of inventive step if combined with one or more other documents of same category.	P	Document published on or after the declared priority date but before the filing date of this invention.
&	Member of the same patent family	E	Patent document published on or after, but with priority date earlier than, the filing date of this application.

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